NUTRITION

Author: Barbul, A.
Title: **Arginine: Biochemistry and therapeutic implications**.
Source: Journal of Parenteral and Enteral Nutrition, 10 (1986) 227-238.

Author: Isidori, A; Lo Monaco, A; et al
Title: **A study of growth hormone release in man after oral administration of amino acids.**.
Source: Current Medical Research and Opinions, 7(1981) 475-481.

Author: Jeserich, M: Munzel, T; et al
Title: **Reduced plasma L arginine in hypercholesterolaemia.**.
Source: The Lancet, 339 (1992) 561.

Author: Kelly, E; Morris, SM; et al
Title: **Nitric oxide, sepsis, and arginine metabolism.**.
Source: Journal of Parenteral and Enteral Nutrition, 19 (1995) 234-238.

Author: Knowles, RG; Palacios, M; et al
Title: **Formationof nitric oxide from L-arginine inthe central nervous system: A transduction mechanism for stimulation of the soluble guanylate cyclase.**.
Source: Proceedings of the National Academy of Sciences (USA), 86 (1989) 5159-5162.

Author(s): Wu G ; Meininger CJ ; Knabe DA ; Bazer FW ; Rhoads JM
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Title:
Arginine nutrition in development, health and disease.
Source: Curr Opin Clin Nutr Metab Care (Curr Opin Clin Nutr Metab Care) 2000 Jan; 3 (1): 59-66
Abstract: As a precursor of nitric oxide, polyamines and other molecules with enormous biologic importance, L-arginine plays versatile key roles in nutrition and metabolism. Arginine is an essential amino acid in the fetus and neonate, and is conditionally an essential nutrient for adults, particularly in certain disease conditions. L-Arginine administration is beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, and in facilitating wound healing. The effect of L-arginine in treating many common health problems is unique among amino acids, and offers great

promise for improved health and well-being in the future.

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Title:
Role of immunonutrition in reducing complications following organ transplantation.

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Source: Transplant Proc (TRANSPLANTATION PROCEEDINGS) 2000 May; 32 (3): 574-5

Title:
Vasoactive substances in the interstitium of contracting skeletal muscle examined by microdialysis.

Source:
Proc Nutr Soc (PROCEEDINGS OF THE NUTRITION SOCIETY) 1999 Nov; 58 (4): 925-33

Abstract:
In the study of the regulation of skeletal muscle blood flow during exercise it is useful to obtain information regarding the concentrations of vasoactive substances in the muscle interstitium, a site where the compounds act on the vascular and skeletal muscle cells. The microdialysis technique is a useful tool for measuring interstitial substances in the muscle at rest and during exercise in human subjects, and the technique can also be used to study the effect of both systemic and local interventions in a specific area of an exercising muscle. Probe recovery, which represents the relative amount of a substance that is diffusing to the dialysis membrane, changes from rest to exercise and can be determined by the internal-standard technique which allows for a relatively high time resolution (min). Furthermore, the use of electrodes at the microdialysis outlet makes it possible to perform continuous measurements of interstitial substances. The present review gives examples of how the microdialysis technique has been applied to study potentially important vasodilators such as adenosine, NO and K+ in human skeletal muscles and highlights areas for future research to establish the functional importance of these compounds.

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Title:

Immunonutrition and surgical practice.

Source: Proc Nutr Soc (PROCEEDINGS OF THE NUTRITION SOCIETY) 1999 Nov; 58 (4): 831-7

Abstract:

Immunonutrition generally refers to the effect of the provision of specific nutrients on the immune system. These nutrients typically have immunoenhancing properties, and recent advances in nutrition support involve studies designed to exploit the desirable biological properties of these nutrients. The term immunonutrition strictly implies that we are focusing on the effect of certain nutrients on aspects of the immune system. However, in reality immunonutrition also refers to studies that not only examine the function of lymphocytes and leucocytes, but which also study the influence of key nutrients on the acute-phase response, the inflammatory response and on gastrointestinal structure and function. The interest, therefore, is on the impact of immunonutrition on all aspects of host defence mechanisms in response to a catabolic stress. Major surgery evokes an acute-phase response, a transient immunosuppression and alterations in gastrointestinal function. Normal function is usually restored after a few days; however, in a subgroup of patients homeostasis may be lost and development of the systemic inflammatory response syndrome (SIRS) ensues. Results of recent clinical trials suggest that provision of immunomodulatory nutrients, including glutamine, arginine, n-3 polyunsaturated fatty acids and dietary nucleotides, may promote restoration of normal tissue function post-operatively and prevent the occurrence of SIRS.

Author:

Cui XL ; Iwasa M ; Iwasa Y ; Ogoshi S

Department of Surgery II, Kochi Medical School, Nankoku, Japan.

Title:

Arginine-supplemented diet decreases expression of inflammatory cytokines and improves survival in burned rats.

JPEN J Parenter Enteral Nutr (JPEN. JOURNAL OF PARENTERAL AND ENTERAL NUTRITION) 2000 Mar-Apr; 24(2): 89-96

Abstract:

BACKGROUND: We examined whether the expression of inflammatory cytokines in organs was influenced by the enteral diet supplemented with arginine in burned rats. METHODS: Male Wistar rats weighing about 200 g underwent catheter jejunostomy and received scald burns covering 30% of the whole-body surface area. Animals were divided into two groups: a control group (no supplemental arginine, n = 12) and an arginine group (supplemental arginine: 7.7 g/L, n = 10), which continuously received total enteral nutrition for 7 days (250 kcal/kg/d, 1.72

gN/kg/d). The following were measured after the experiment: (1) messenger RNA (mRNA) expression of tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), interleukin-1beta (IL-1beta), and IL-6 in the spleen, thymus, lung, and liver by a semiquantitative reverse transcription-polymerase chain reaction method, (2) inflammatory cytokines in the plasma and supernatant of cultured splenic lymphocytes by enzyme-linked immunosorbant assay, (3) nitric oxide (NO) product, NO2-/NO3-, in the plasma and supernatant of cultured splenic lymphocytes by the Griess method, and (4) survival rate by the Kaplan-Meier method. RESULTS: The mRNA expression of TNF-alpha was significantly decreased in the spleen and lung ($p < .01$, $p < .05$), IFN-gamma in the lung ($p < .05$), IL-1beta in the spleen ($p < .05$), and IL-6 in the thymus and liver ($p < .05$, $p < .05$) in the arginine group when compared with the control group. The production of TNF-alpha by splenic lymphocytes was suppressed in the arginine group in both concanavalin A (Con A)-treated and -untreated cultures ($p < .01$, $p < .05$). The production of IFN-gamma by splenic lymphocytes treated with Con A was suppressed in the arginine group ($p < .05$). The NO product in the supernatant without Con A was increased in the arginine group ($p < .05$). The mortality rate of the arginine group (0%) was lower than that in the control group (33.3%) on day 7 after the burn injury ($p < .05$). CONCLUSIONS: The data suggest that dietary arginine supplementation decreases the mRNA expression of inflammatory cytokines in organs and improves the survival rate after thermal injury.

Author:

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Title:

Metallothionein, nitric oxide and zinc homeostasis in vascular endothelial cells. J Nutr (JOURNAL OF NUTRITION) 2000 May; 130 (5S Suppl): 1467S-70S

Abstract:

Recent in vitro studies suggest that the oxidoreductive capacity of metal thiolate clusters in metallothionein (MT) contributes to intracellular zinc homeostasis. We used fluorescence-based techniques to address this hypothesis in intact endothelial cells, focusing on the contributory role of the important redox signaling molecule, nitric oxide. Microspectrofluorometry with Zinquin revealed that the exposure of cultured sheep pulmonary artery endothelial cells to S-nitrosocysteine resulted in the release of N, N,N',N'-tetrakis(2. pyridylmethyl)ethylendiamine (TPEN) chelatable zinc. Cultured sheep pulmonary artery endothelial cells were transfected with a plasmid expression vector suitable for fluorescence resonance energy transfer containing the cDNA of MT sandwiched between two mutant green fluorescent proteins. The exposure of cultured sheep pulmonary artery endothelial cells transfected with this chimera to nitric oxide donors or to agents that increased cytoplasmic Ca(2+) via endogenously generated nitric oxide decreased the

efficiency of fluorescence resonance energy transfer in a manner consistent with the release of metal (Zn) from MT. A physiological role for this interaction in intact tissue was supported by the lack of myogenic reflex in resistance arteries of MT knockout mice unless endogenous nitric oxide synthesis was blocked. These data suggest an important role for metal thiolate clusters of MT in nitric oxide signaling in the vascular wall.

Author:

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Title:

Zinc deficiency, malnutrition and the gastrointestinal tract. J Nutr (JOURNAL OF NUTRITION) 2000 May; 130 (5S Suppl): 1388S-92S

Abstract:

Recent clinical and experimental findings have reinforced the link among zinc deficiency, malnutrition and diarrheal disease. Because there is a strong association between protein and zinc content in virtually all types of foods, insufficient protein intake may often be the cause of zinc deficiency. Compensatory mechanisms operating in monogastric species during malnutrition are less effective for the absorption of transition divalent elements such as zinc, which remain bound to ligands of dietary or endogenous origin. Both protein and zinc deficiencies are strong negative determinants for normal cellular immunity. In zinc deficiency, the organism is more susceptible to toxin-producing bacteria or enteroviral pathogens that activate guanylate and adenylate cyclases, stimulating chloride secretion, producing diarrhea and diminishing absorption of nutrients, thus exacerbating an already compromised mineral status. In addition, zinc deficiency may impair the absorption of water and electrolytes, delaying the termination of normally self-limiting gastrointestinal disease episodes. The gastrointestinal tract may be one of the first target areas where zinc insufficiency may be manifested. A prolonged low zinc intake deprives the organism of the local potential beneficial effects of zinc, including interactions with oxidative free radicals and nitric oxide metabolism. Nitric oxide is a second messenger that plays an important part in the triggering of diarrheal disease. The possible interrelationship among infection, inflammation, free radical damage and its quenching by potential scavengers, such as zinc, in the intestinal lumen or within the enterocyte should be more extensively studied.

Author:

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Title:

Complications of pancreatic surgery and the role of perioperative nutrition. Dig Surg (DIGESTIVE SURGERY) 1999; 16 (4): 320-6

Abstract:

BACKGROUND: According to international guidelines, artificial nutrition may be indicated after pancreaticoduodenectomy (PD). This clinical study was designed to evaluate whether the route of administration and the composition of the postoperative nutritional support could affect outcome. METHODS: One hundred patients who underwent PD for cancer of the pancreatic head were prospectively studied. Patients were randomized to receive a standard enteral formula (SEN; n = 35) or immunonutrition with an enteral formula enriched with arginine, omega-3 fatty acids, and RNA (IEN group; n = 33), or total parenteral nutrition (TPN; n = 32). Postoperative feeding was started within 12 h after surgery. The three regimens were isoenergetic and isonitrogenous. Tolerance of enteral feeding, rate and severity of postoperative complications, and length of hospital stay (LOS) were evaluated. RESULTS: Full nutritional goal (25 kcal/kg) was achieved in 84% of enterally fed patients versus 96% in the parenteral group (p = NS). The rate of postoperative complications was lower in the IEN group (33%) than in the SEN (40%) and TPN groups (59%). The severity of infectious complications (sepsis score) was lower in the IEN (5.5) than the SEN (7.9) and TPN groups (10.4; $p < 0.05$). LOS was shorter in the IEN than in the SEN and TPN groups (16.3 vs. 17.8 vs. 19.3 days, respectively; $p < 0.05$). CONCLUSIONS: In patients undergoing PD the established nutritional goal can be obtained by enteral feeding. Immunonutrition seems to improve outcome.

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Title: **[Brain hypothermia treatment for the management of severe pediatric brain injury]**

Source: No To Hattatsu (NO TO HATTATSU [BRAIN AND DEVELOPMENT]) 2000 Mar; 32 (2): 122-31

Language: JAPANESE

Abstract: In the management of severe pediatric brain injury, attention has previously been paid to brain edema, ICP elevation and low cerebral perfusion pressure (CPP). However, in the acute stage within 3-6 hours after trauma, brain hypoxia and hyperglycemia associated with diffuse brain injury are often observed. We have pointed out brain thermo-pooling (elevation of brain tissue temperature) and brain hypoxia caused by defective release of oxygen from hemoglobin (due to decrease in red blood cell enzyme (DPG)) as a new mechanism of brain injury.

To treat these pathologic changes, we have developed a brain hypothermia treatment, the major purpose of which is to prevent brain hypoxia, brain thermo-pooling, neurohormonal changes causing cytokine encephalopathy, and a selective, radical-mediated damage of the dopamine A10 nervous system. The brain tissue temperature is initially adjusted to 35 degrees C with adequate cerebral oxygenation, followed by brain hypothermia at 34 degrees C for 1 weeks to prevent brain hypoxia, free radical reactions, brain edema and ICP elevation. What is most difficult in the pediatric brain hypothermia treatment is to maintain metabolic balance in the injured brain tissue and pulmonary infections associated with an immune crisis. When a rapid elevation of serum glucose is noted it is critical to lower the value because glucose quickly penetrates the blood-brain barrier and increases pyruvate and lactate by inhibiting the TCA cycle metabolism. Thus, hyperglycemia during brain hypothermia treatment is one of the major target of management. Another problem is immune crisis associated with secondary pulmonary infections. To prevent them, early enteral nutrition and replacement of L-arginine were most useful, as well as preconditioning for rewarming as follows: serum albumin > 3.0 g/dl; lymphocyte > 1500/mm3; T-H (CD4) lymphocytes > 55%; serum glucose, 120-140 mg/dl; vitamin A > 50 mg/dl; Hb > 12 g/dl and 2,3 DPG, 10-15 mumol/gHb; O2 ER, 23-25% and AT-III, > 100%. The clinical benefit of this therapy is still controversial.

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Title: **An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients [see comments]**

Source: Crit Care Med (CRITICAL CARE MEDICINE) 2000 Mar; 28 (3): 643-8

Abstract: OBJECTIVE: To determine whether early enteral

feeding in a septic intensive care unit (ICU) population, using a formula supplemented with arginine, mRNA, and omega-3 fatty acids from fish oil (Impact), improves clinical outcomes, when compared with a common use, high protein enteral feed without these nutrients. DESIGN: A prospective, randomized, multicentered trial. SETTING: ICUs of six hospitals in Spain. PATIENTS: One hundred eighty-one septic patients (122 males, 59 females) presenting for enteral nutrition in an ICU. INTERVENTIONS: Septic ICU patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores of > or =10 received either an enteral feed enriched with arginine, mRNA, and omega-3 fatty acids from fish oil (Impact), or a common use, high protein control feed (Precitene Hiperproteico). MEASUREMENTS AND MAIN RESULTS: One hundred seventy-six (89 Impact patients, 87 control subjects) were eligible for intention-to-treat analysis. The mortality rate was reduced for the treatment group compared with the control group (17 of 89 vs. 28 of 87; $p < .05$). Bacteremias were reduced in the treatment group (7 of 89 vs. 19 of 87; $p = .01$) as well as the number of patients with more than one nosocomial infection (5 of 89 vs. 17 of 87; $p = .01$). The benefit in mortality rate for the treatment group was more pronounced for patients with APACHE II scores between 10 and 15 (1 of 26 vs. 8 of 29; $p = .02$). CONCLUSIONS: Immune-enhancing enteral nutrition resulted in a significant reduction in the mortality rate and infection rate in septic patients admitted to the ICU. These reductions were greater for patients with less severe illness.

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Title: **Role of nitric oxide and peroxynitrite in bile salt-induced apoptosis: relevance to colon carcinogenesis.**

Source: Nutr Cancer (NUTRITION AND CANCER) 1999; 35 (2): 180-8

Abstract: Previous work from our laboratory indicated that the bile salt sodium deoxycholate (NaDOC) induced apoptosis in cultured cells and in normal goblet cells of the colonic mucosa. We also reported that the normal-appearing flat mucosa of patients with colon cancer exhibited apoptosis resistance. Using immunofluorescence in conjunction with confocal microscopy, we now report that high physiological concentrations (0.5 mM) of NaDOC result in the formation of nitrotyrosine residues, a footprint for the formation of reactive nitrogen species, including peroxynitrite, in plasma membrane-associated proteins of HT-29 cells. Because peroxynitrite is formed from the reaction between nitric oxide and superoxide anion, we specifically looked at the role of nitric oxide and superoxide anion in NaDOC-induced apoptosis. Pretreatment of cells with the inhibitor/antioxidants, N-nitro-L-arginine methyl ester, an inhibitor of nitric oxide synthase, copper (II) 3,5-diisopropyl salicylate hydrate, a superoxide dismutase mimetic compound, and Trolox, a water-soluble analog of alpha-tocopherol, alone or in combination, sensitized cells to apoptosis induced by 0.5 mM NaDOC. These results suggest that nitric oxide may be part of a signaling pathway that is responsible for apoptosis resistance. The results also indicate that nitric oxide does not appear to protect cells against NaDOC-induced apoptosis by scavenging superoxide anion.

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Title: **Amino acid supplements to improve athletic performance.**

Source: Curr Opin Clin Nutr Metab Care (Curr Opin Clin Nutr Metab Care) 1999 Nov; 2 (6): 539-44

Abstract: This review provides a critical evaluation of the metabolic rationale for the use of individual amino acids as nutritional ergogenic (work-generating) aids in athletes. The conclusion is that in contrast to the claims made on sport nutrition products, branched-chain amino acids do not improve endurance performance, that the evidence that glutamine supplements may improve immune function is rather weak, and that the available commercial supplements contain too little arginine to increase growth hormone levels. No studies have been performed to investigate the claim that tyrosine supplements can improve explosive exercise.

Author(s): Cui L ; Takagi Y ; Sando K ; Wasa M ; Okada A
Address: Department of Pediatric Surgery, Osaka University Medical School, Japan.
Title: **Nitric oxide synthase inhibitor attenuates inflammatory lesions in the skin of zinc-deficient rats.**
Source: Nutrition (NUTRITION) 2000 Jan; 16 (1): 34-41

Abstract: Skin lesions are common manifestations of zinc deficiency in humans and animals, but the pathogenic mechanisms have not been fully clarified. In the present study, a nitric oxide synthase inhibitor, NG-nitro-L-arginine methyl ester (L-NAME), was given to zinc-deficient (ZD) rats to see whether it prevents or delays the occurrence of skin lesions. Weanling male rats were given free access to a ZD diet (2 mg zinc/kg) for 4 wk to induce zinc deficiency. Control rats, including pair-fed (PF) and ad libitum (AL) groups, were given a diet supplemented with zinc (50.8 mg zinc/kg. L-NAME (0.3 g/L in drinking water) was given to some ZD rats for 3 wk, starting at the second week of their ZD dieting. Dermatitis of the extremities, balanitis, stomatitis, and alopecia appeared in ZD but not in AL and PF rats. Administration of L-NAME significantly reduced the frequency of cutaneous and mucocutaneous inflammatory lesions but did not prevent alopecia in the ZD rats. Reverse transcription polymerase

chain reaction showed that inducible nitric oxide synthase mRNA was expressed in the paw skin of ZD but not of AL and PF rats. Evaluation of skin microvascular permeability by the Evans blue leakage technique indicated that L-NAME administration significantly attenuated extravasation of Evans blue in the paw skin of ZD rats. Furthermore, stains positive for terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling were condensed and diffusely distributed over the epidermis, dermis, and subcutaneous tissue of paws in ZD rats. ZD rats had intense cell infiltration and parakeratosis in the paw skin. L-NAME administration effectively prevented these morphologic changes. These results demonstrate that nitric oxide synthase inhibitor ameliorates inflammatory lesions of the skin in ZD rats.

Author(s): Hsu CM ; Liu CH ; Chen LW
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Title: **Nitric oxide synthase inhibitor ameliorates oral total parenteral nutrition-induced barrier dysfunction.**
Source: Shock (SHOCK) 2000 Feb; 13 (2): 135-9 Journal Code: CAE
Additional Info: UNITED STATES
Standard No: ISSN: 1073-2322
Language: ENGLISH
Abstract: The expression of inducible nitric oxide synthase (iNOS) is increased in the intestine and results in mucosal damage after endotoxin challenge. Although the oral administration of total parenteral nutrition (TPN) solution promotes bacterial translocation (BT) and increases the intestinal permeability, the role of NO in the nutrition-induced loss of mucosal barrier function remains unclear. The distribution of fluorescein isothiocyanate-dextran (FITC-dextran, 4400) across the lumen of small intestine in rat was examined to investigate the role of NOS activity on the intestinal permeability under oral TPN feeding.

Fifty-one rats were randomly divided into 4 groups. Group I (control group) was fed with rat chow, group II received TPN solution orally. Groups III and IV received TPN solution supplemented with NOS inhibitors. On day 9, FITC-dextran was injected into the intestinal lumen. After 30 min, blood samples were taken from portal vein and analyzed for plasma FITC-dextran level by fluorescence spectrophotometry. Samples of small intestine were frozen and sectioned in a cryostat for morphological and NOS histochemical studies. Homogenates of small intestine were used for NOS activity measurement. The plasma level of FITC-dextran showed a significant increase ($P < 0.05$) in rats fed with oral TPN compared with the control ones. Supplement with NOS inhibitors significantly decreased the intestinal permeability in groups III and IV compared with group II. Similarly, the total NOS activities showed a significant 2-fold increase ($P< 0.05$) in group II, and NOS inhibitors decreased the elevated NOS activity. These data suggest that oral TPN feeding for 9 days leads to an increase in permeability to dextran and the total NOS activity of small intestine, and both induction of the intestinal permeability and NOS activity were inhibited by treatment with NOS inhibitors. Addition of S-methylisothiourea (SMT), an iNOS selective inhibitor, profoundly inhibited 66% of the induced iNOS activity ($P < 0.05$) and reduced 74% of the diet-induced increase in intestinal permeability ($P < 0.05$) in group II. The induced permeability change in rats receiving oral TPN is mainly due to the activity of intestinal mucosal iNOS. The induction of iNOS is an important mediator for intestinal barrier dysfunction. Administration of SMT, which specifically decreases iNOS activity, is useful in the prevention of diet-induced barrier failure.

Author(s): Clavell M ; Correa-Gracian H ; Liu Z ; Craver R ; Brown R ; Schmidt-Sommerfeld E ; Udall J Jr ; Delgado A ; Mannick E

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Title: **Detection of interferon regulatory factor-1 in lamina propria mononuclear cells in Crohn's disease.**

Source: J Pediatr Gastroenterol Nutr (JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION) 2000 Jan; 30 (1): 43-7

Abstract: BACKGROUND: The transcription factor, interferon regulatory factor (IRF)-1, is stimulated by interferon-gamma and regulates the expression of several genes implicated in the pathogenesis of inflammatory bowel disease, including interleukin-6, major histocompatibility complex class II molecules, and inducible nitric oxide synthase. Interferon regulatory factor-1 also stimulates naive CD4+ T-cells to differentiate into T-helper-1 cells, the T-cell subset that appears to be upregulated in Crohn's disease. The purpose of this study was to examine the expression of IRF-1 in the nuclei of lamina propria mononuclear cells in situ in colonoscopic biopsy specimens from pediatric patients with Crohn's disease, in patients with ulcerative colitis, and in control patients with no histopathologic abnormalities. METHODS: Archival paraffin-embedded tissue sections were obtained from 25 pediatric patients with Crohn's disease, 6 patients with ulcerative colitis, and 12 control patients who had undergone colonoscopy. Tissue sections were stained with polyclonal rabbit anti-human antisera to IRF-1 and horseradish-peroxidase-conjugated, biotinylated, goat anti-rabbit secondary antibody. Slides were scored and scores compared among patient groups using analysis of variance. RESULTS: Patients with Crohn's disease had significantly higher IRF-1 scores (95% confidence interval [CI], 1.70-2.04) than patients with ulcerative colitis (95% CI, 0.92-1.23) or control subjects (95% CI, 1.11-1.52). CONCLUSIONS: Increased expression of IRF-1 in lamina propria mononuclear cells from patients with Crohn's disease may be relevant to the pathogenesis

of Crohn's disease.

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Title: **Immunonutrition in the critically ill: a systematic review of clinical outcome.**
Source: Crit Care Med (CRITICAL CARE MEDICINE) 1999 Dec; 27 (12): 2799-805 Journal Code: DTF
Additional Info: UNITED STATES
Standard No: ISSN: 0090-3493
Language: ENGLISH
Abstract: OBJECTIVE: To perform a meta-analysis addressing whether enteral nutrition with immune-enhancing feeds benefits critically ill patients after trauma, sepsis, or major surgery. DATA SOURCES: Studies were identified by MEDLINE search (1967 to January 1998) for original articles in English using the search terms "human," "enteral nutrition," "arginine," "nucleotides," "omega-3 fatty acids," "immunonutrition," "IMPACT," and "Immun-Aid." Additionally, the authors of the studies and the manufacturers of the feeds were contacted for additional information. Access to original databases was obtained for the three largest studies. STUDY SELECTION: Fifteen randomized controlled trials comparing patients receiving standard enteral nutrition with patients receiving a commercially available immune-enhancing feed with arginine with or without glutamine, nucleotides, and omega-3 fatty acids were identified by two independent reviewers (Dr. Beale and Dr. Bryg). DATA EXTRACTION: Descriptive and outcome data were extracted independently from the papers by the same two reviewers, one of whom (Dr. Bryg) analyzed the original databases. Three studies were excluded from analysis, leaving 12 studies containing 1,557 subjects, 1,482 of whom were analyzed. Main outcome measures were mortality, infection, ventilator days, intensive care unit stay, hospital stay, diarrhea days, calorie intake, and nitrogen intake. The

meta-analysis was performed on an intent-to-treat basis. DATA SYNTHESIS: There was no effect of immunonutrition on mortality (relative risk = 1.05, confidence interval [CI] = 0.78, 1.41; p = .76). There were significant reductions in infection rate (relative risk = 0.67, CI = 0.50, 0.89; p = .006), ventilator days (2.6 days, CI = 0.1, 5.1; p = .04), and hospital length of stay (2.9 days, CI = 1.4, 4.4; p = .0002) in the immunonutrition group. CONCLUSIONS: The benefits of enteral immunonutrition were most pronounced in surgical patients, although they were present in all groups. The reduction in hospital length of stay.

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Title: **Amino acid limitation regulates gene expression.**
Source: Proc Nutr Soc (PROCEEDINGS OF THE NUTRITION SOCIETY) 1999 Aug; 58 (3): 625-32
Abstract: In mammals, the plasma concentration of amino acids is affected by nutritional or pathological conditions. For example, an alteration in the amino acid profile has been reported when there is a deficiency of any one or more of the essential amino acids, a dietary imbalance of amino acids, or an insufficient intake of protein. We examined the role of amino acid limitation in regulating mammalian gene expression. Depletion of arginine, cystine and all essential amino acids leads to induction of insulin-like growth factor-binding protein-1 (IGFBP-1) mRNA and protein expression in a dose-dependent manner. Moreover, exposure of HepG2 cells to amino acids at a concentration reproducing the amino acid concentration found in portal blood of rats fed on a low-protein diet leads to a significantly higher ($P < 0.0002$) expression of IGFBP-1. Using CCAAT/enhancer-binding protein homologous protein (CHOP) induction by leucine deprivation as a model, we have characterized the molecular mechanisms involved in the regulation of gene expression by amino acids.

We have shown that leucine limitation leads to induction of CHOP mRNA and protein. Elevated mRNA levels result from both an increase in the rate of CHOP transcription and an increase in mRNA stability. We have characterized two elements of the CHOP gene that are essential to the transcriptional activation produced by an amino acid limitation. These findings demonstrate that an amino acid limitation, as occurs during dietary protein deficiency, can induce gene expression. Thus, amino acids by themselves can play, in concert with hormones, an important role in the control of gene expression.

Author(s): McCarty MF ; Russell AL
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Title: **Niacinamide therapy for osteoarthritis--does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes?**
Source: Med Hypotheses (MEDICAL HYPOTHESES) 1999 Oct; 53 (4): 350-60
Abstract: Fifty years ago, Kaufman reported that high-dose niacinamide was beneficial in osteoarthritis (OA) and rheumatoid arthritis. A recent double-blind study confirms the efficacy of niacinamide in OA. It may be feasible to interpret this finding in the context of evidence that synovium-generated interleukin-1 (IL-1), by inducing nitric oxide (NO) synthase and thereby inhibiting chondrocyte synthesis of aggrecan and type II collagen, is crucial to the pathogenesis of OA. Niacinamide and other inhibitors of ADP-ribosylation have been shown to suppress cytokine-mediated induction of NO synthase in a number of types of cells; it is therefore reasonable to speculate that niacinamide will have a comparable effect in IL-1-exposed chondrocytes, blunting the anti-anabolic impact of IL-1. The chondroprotective antibiotic doxycycline may have a similar mechanism of action. Other nutrients reported to be useful in OA may likewise intervene in the activity or synthesis of IL-1. Supplemental glucosamine can be expected to

stimulate synovial synthesis of hyaluronic acid; hyaluronic acid suppresses the anti-catabolic effect of IL-1 in chondrocyte cell cultures, and has documented therapeutic efficacy when injected intra-articularly. S-adenosylmethionine (SAM), another proven therapy for OA, upregulates the proteoglycan synthesis of chondrocytes, perhaps because it functions physiologically as a signal of sulfur availability. IL-1 is likely to decrease SAM levels in chondrocytes; supplemental SAM may compensate for this deficit. Adequate selenium nutrition may down-regulate cytokine signaling, and ample intakes of fish oil can be expected to decrease synovial IL-1 production; these nutrients should receive further evaluation in OA. These considerations suggest that non-toxic nutritional regimens, by intervening at multiple points in the signal transduction pathways that promote the synthesis and mediate the activity of IL-1, may provide a substantially superior alternative to NSAIDs (merely palliative and often dangerously toxic) in the treatment and perhaps prevention of OA.

CARDIOLOGY

Author: Boder-Boger, SM; Boger RH et. al.
Title: **L-Arginine induces nitric oxide-dependent vasodilation in patients with critical limb ischemia: A randomized controlled study.**
Source: Circulation, 93 (1996) 89-95.

Author: Drexler, H; Zeiher, AM; et al.
Title: **Correctionof endothelial dysfunction in coronary microcirculation of Hypercholesterolaemic patients by L-arginine**.
Source: The Lancet, 338 (1991) 1546-1550.

Author: Egashira, K; Hirooka, Y; et al.
Title: **Effects of L-arginine supplementation on endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary arteriograms**.
Source: Nature, 263 (1994) 466.

Author: Hamon, M; Valet, B; et al
Title: **Long term oral administration of L-arginine reduces intimal thickening and enhances neoendothelium-dependent acethylcholine-induced relaxation after arterial injury**.
Source: Circulation, 90 (1994) 1357-1362.

Author: Hishikawa, K Nakaki, T; et al

Title: **L-arginine as an antihypertensive agent.**.
Source: Journal of Cardiovascular Pharmacology, Supplement 12 (1992) 20, S196-197.

Author: Hishikawa, K Nakaki, T; et al
Title: **Effect of systemic L-arginine administration on hemodynamics and nitric oxide release in man.**.
Source: Japan Heart Journal, 33 (1992) 41-48.

Author: Lerman, A; McKinley, L; et al
Title: **Oral chronic L-arginine administration improves coronary endothelial function in humans**.
Source: Supplement to the Journal of the american College of Cardiology 29(1997) 192A-193A.

Author(s):
Bocchi EA ; Vilella de Moraes AV ; Esteves-Filho A ; Bacal F ; Auler JO ; Carmona MJ ; Bellotti G ; Ramires AF
Address: Heart Institute, Medical School of São Paulo University, Brazil.

Title:
L-arginine reduces heart rate and improves hemodynamics in severe congestive heart failure.

Source:
Clin Cardiol (CLINICAL CARDIOLOGY) 2000 Mar; 23 (3): 205-10

Abstract:
BACKGROUND: Stimulated endothelium-derived relaxing factor-mediated vasodilation and conduit artery distensibility are impaired in congestive heart failure (CHF). L-arginine could have a potentially beneficial role in CHF, acting through the nitric oxide (NO)-L-arginine pathway or by growth hormone increment. HYPOTHESIS: This study was undertaken to investigate the effects of L-arginine on heart rate, hemodynamics, and left ventricular (LV) function in CHF. METHODS: In seven patients (aged 39 +/- 8 years) with CHF, we obtained the following parameters using echocardiography and an LV Millar Mikro-Tip catheter simultaneously under four conditions: basal, during NO inhalation (40 ppm), in basal condition before L-arginine infusion, and after L-arginine intravenous infusion (mean dose 30.4 +/- 1.9 g). RESULTS: Nitric oxide inhalation increased pulmonary capillary wedge pressure from 25 +/- 9 to 31 +/- 7 mmHg ($p < 0.05$), but did not change echocardiographic variables or LV contractility by elastance determination. L-arginine decreased heart rate (from 88 +/- 15 to 80 +/- 16 beats/min, $p<0.005$), mean systemic arterial pressure (from 84 +/- 17 to 70 +/- 18 mmHg, $p < 0.007$), and systemic vascular resistance (from 24 +/- 8 to 15 +/- 6 Wood units, $p<0.003$). L-arginine increased right atrial pressure (from 7 +/- 2 to 10 +/- 3 mmHg, $p<0.04$), cardiac output (from 3.4 +/- 0.7 to 4.1 +/- 0.8 l/min, $p < 0.009$), and stroke volume (from 40 +/- 9 to 54 +/- 14 ml, $p < 0.008$). The ratios of pulmonary vascular resistance to systemic vascular resistance at baseline and during NO inhalation were

0.09 and 0.075, respectively, and with L-arginine this increased from 0.09 to 0.12. CONCLUSION: L-arginine exerted no effect on contractility; however, by acting on systemic vascular resistance it improved cardiac performance. L-arginine showed a negative chronotropic effect. The possible beneficial effect of L-arginine on reversing endothelial dysfunction in CHF without changing LV contractility should be the subject of further investigations.

Author(s):
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Title:
Nitric oxide in the pathogenesis of vascular disease.
Source:
J Pathol (JOURNAL OF PATHOLOGY) 2000 Feb; 190 (3): 244-54
Abstract:
Nitric oxide (NO) is synthesized by at least three distinct isoforms of NO synthase (NOS). Their substrate and cofactor requirements are very similar. All three isoforms have some implications, physiological or pathophysiological, in the cardiovascular system. The endothelial NOS III is physiologically important for vascular homeostasis, keeping the vasculature dilated, protecting the intima from platelet aggregates and leukocyte adhesion, and preventing smooth muscle proliferation. Central and peripheral neuronal NOS I may also contribute to blood pressure regulation. Vascular disease associated with hypercholesterolaemia, diabetes, and hypertension is characterized by endothelial dysfunction and reduced endothelium-mediated vasodilation. Oxidative stress and the inactivation of NO by superoxide anions play an important role in these disease states. Supplementation of the NOS substrate L-arginine can improve endothelial dysfunction in animals and man. Also, the addition of the NOS cofactor (6R)-5,6,7, 8-tetrahydrobiopterin improves endothelium-mediated vasodilation in certain disease states. In cerebrovascular stroke, neuronal NOS I and cytokine-inducible NOS II play a key role in neurodegeneration, whereas endothelial NOS III is important for maintaining cerebral blood flow and preventing neuronal injury. In sepsis, NOS II is induced in the vascular wall by bacterial endotoxin and/or cytokines. NOS II produces large amounts of NO, which is an important mediator of endotoxin-induced arteriolar vasodilatation, hypotension, and shock. Copyright 2000 John Wiley & Sons, Ltd.

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Title:
Enhanced NO inactivation and hypertension induced by a high-fat, refined-carbohydrate diet.
Source:
Hypertension (HYPERTENSION) 2000 Sep; 36 (3): 423-9
Abstract:
We have recently demonstrated that long-term consumption of a high-fat, refined-carbohydrate (HFS) diet induces hypertension (HTN) in normal rats

compared with a low-fat, complex-carbohydrate (LFCC) diet. Limited evidence suggests that high-fat or high-sugar diets cause enhanced generation of reactive oxygen species (ROS). We therefore hypothesized that by inducing oxidative stress, the HFS diet may promote nitric oxide (NO) inactivation and HTN. To test this hypothesis, female Fischer rats were placed on either the HFS or the LFCC diet starting at 2 months of age. Blood pressure, urinary NO metabolites (NO(x)), and total renal NO synthase activity were monitored, and the tissue abundance of nitrotyrosine (NT), which is the stable "footprint" of NO oxidation by ROS, was determined. The HFS diet group exhibited a gradual rise in arterial blood pressure and were hypertensive by 18 months. This trend was accompanied by a marked accumulation of NT in all tested tissues, an initial rise and a subsequent fall in NO synthase activity, and a fall in urinary NO(x) excretion. The HFS diet-fed animals had a blunted blood pressure response to the NO synthase inhibitor N:(omega)-nitro-L-arginine methyl ester (L-NAME) compared with the LFCC diet group, which showed a marked hypertensive response to L-NAME. L-NAME-induced HTN was reversible with L-arginine in the LFCC diet group; however, HTN was not corrected by L-arginine supplementation in the HFS diet group. These findings point to enhanced ROS-mediated inactivation and sequestration of NO, which may contribute to the reduction of bioactive NO and HTN in the HFS diet-fed animals.

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Title:
Blood pressure and metabolic changes during dietary L-arginine supplementation in humans.

Source:
Am J Hypertens (AMERICAN JOURNAL OF HYPERTENSION) 2000 May; 13 (5 Pt 1): 547-51

Abstract:
Dietary L-arginine supplementation has been proposed to reverse endothelial dysfunction in such diverse pathophysiologic conditions as hypercholesterolemia, coronary heart disease, and some forms of animal hypertension. In particular, chronic oral administration of L-arginine prevented the blood pressure rise induced by sodium chloride loading in salt-sensitive rats. To investigate the effects of L-arginine-rich diets on blood pressure and metabolic and coagulation parameters we performed a single-blind, controlled, crossover dietary intervention in six healthy volunteers. The subjects (aged 39+/-4 years, body mass index [BMI] 26+/-1 kg/m2, mean +/- SEM) received, in random sequence, three different isocaloric diets, each for a period of 1 week (Diet 1: control; Diet 2: L-arginine enriched by natural foods; Diet 3: identical to Diet 1 plus oral L-arginine supplement). Sodium intake was set at a constant level (about 180 mmol/day) throughout the three study periods. A blood pressure decrease was observed with both L-arginine-rich diets (Diet 2 v 1, SBP: -6.2 mm Hg [95% CI: -0.5 to -11.8], DBP: -5.0 mm Hg [-2.8 to -7.2]; Diet 3 v 1, SBP: -6.2 mm Hg [-1.8 to -10.5], DBP: -6.8 mm Hg [-3.0 to -10.6]). A slight increase in creatinine clearance (P = .07) and a fall in fasting blood glucose (P = .008) occurred after Diet 3 and, to a lesser extent, after Diet 2. Serum total cholesterol (P = .06) and triglyceride (P = .009) decreased and HDL cholesterol increased (P = .04) after Diet 2, but not after Diet 3. These results

indicate that a moderate increase in L-arginine significantly lowered blood pressure and affected renal function and carbohydrate metabolism in healthy volunteers.

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Title:
Baroreceptor dysfunction induced by nitric oxide synthase inhibition in humans.
Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 2000 Jul; 36 (1): 213-8
Abstract:
OBJECTIVES: We sought to investigate baroreceptor regulation of sympathetic nerve activity and hemodynamics after inhibition of nitric oxide (NO) synthesis. BACKGROUND: Both the sympathetic nervous system and endothelium-derived substances play essential roles in cardiovascular homeostasis and diseases. Little is known about their interactions. METHODS: In healthy volunteers, we recorded muscle sympathetic nerve activity (MSA) with microneurography and central hemodynamics measured at different levels of central venous pressure induced by lower body negative pressure. RESULTS: After administration of the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA, 1 mg/kg/min), systolic blood pressure increased by 24 mm Hg ($p = 0.01$) and diastolic blood pressure by 12 mm Hg ($p = 0.009$), while stroke volume index (measured by thermodilution) fell from 53 to 38 mL/min/m2 ($p < 0.002$). Administration of L-NMMA prevented the compensatory increase of heart rate, but not MSA, to orthostatic stress. The altered response of heart rate was not due to higher blood pressure, because heart rate responses were not altered during infusion of the alpha-1-adrenoceptor agonist phenylephrine (titrated to an equal increase of systolic blood pressure). In the presence of equal systolic blood pressure and central venous pressure, we found no difference in MSA during phenylephrine and L-NMMA infusion. CONCLUSIONS: This study demonstrates a highly specific alteration of baroreceptor regulation of heart rate but not muscle sympathetic activity after inhibition of NO synthesis in healthy volunteers. This suggests an important role of NO in reflex-mediated heart rate regulation in humans.

Author(s):
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Title:
[The cardiovascular significance of nitric oxide] Implicatiile cardio-vasculare ale oxidului nitric.
Source:
Rev Med Chir Soc Med Nat Iasi (REVISTA MEDICO-CHIRURGICALA A SOCIETATII DE MEDICI SI NATURALISTI DIN IASI) 1999 Jul-Dec; 103 (3-4): 48-56
Abstract:
Nitric oxide (NO) synthesized from L-arginine is a ubiquitous intercellular chemical messenger involved in signal transduction in diverse mammalian cells. The isolation of molecular clones for

NO synthases has permitted the characterization of several distinct enzyme isoforms. NO synthesized in vascular endothelial cells plays an important role in the control of vascular tonus and platelet aggregation, through the activation of guanylate-cyclase activity in target tissues mediated by NO. Nitric oxide which is produced by cytokine activated mononuclear cells plays an important role in inflammation and immunity as a cytotoxic effector molecule and as a transducer molecule in immune cells and in oxidative stress as a potential source of intracellular free radicals. An increase in reactive oxygen species can produce damage to lipids, proteins and DNA and induce necrosis or apoptosis. The implication of NO in different pathological processes, such as atherosclerosis, diabetes, ischaemia and reperfusion, or during inflammatory processes and the generation of free radicals contributing to the endothelial injury associated to these processes.

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Title:
ATP sensitive potassium channel and myocardial preconditioning.

Source:
Acta Anaesthesiol Sin (ACTA ANAESTHESIOLOGICA SINICA) 1999 Sep; 37 (3): 121-31

Abstract:
KATP channels play an important role in physiology and pathophysiology of many tissues. As in the pancreatic beta cells, they couple the change of blood glucose with insulin release. The data coming from Baukrowitz et al. and Shyng and Nichols gave the possible answers to the two old enigmas of KATP channels, i.e., different ATP sensitivity reported in the same tissue and how the channel opened under intracellular millimolar ATP concentration, in which they showed the lipids and lipid metabolites are essential for KATP channel regulation by altering ATP sensitivity. This new information rises several further considerations. How does PIP2 reduce the sensitivity of the channel to ATP? In order to clarify the possibility of direct competing or allosteric effect on the ATP binding site, competitive binding assay should be performed. Since the PIP2 theory seems to be the key event to determine the ATP sensitivity and thus control the channel open probability, then what is the resting concentration of PIP2 in the cell membrane? Is it sufficient to account for the difference in the ATP sensitivity of the intact cell and excised patch from different tissues? Quantitative studies either immunoblotting by PIP2 antibody or fluorescence-labeled lipid assay-may obtain some basic but useful data for further studies to answer these questions. Furthermore, the ATPi mediated restoration of activity was inhibited by antibodies against PIP2. The dualistic behavior of KATP channels to intracellular NDPs should be reexamined with respect to PIP2. The vast majority of preconditioning studies has

been performed in intact animals in which myocardial infarct size was used as the end point to define the cardio-protective effect of ischemic PC. These results suggest a key role for the KATP channel as both a trigger and as an end effector of both acute and delayed ischemic PC. The persistent activation of KATP channels during the early reperfusion phase is essential for a smooth and full recovery of contractile function, as well as for maintenance of electrical stability in heart that has been exposed to ischemia. Though activate adenosine A1 receptor coupled with Gi protein can open the KATP channels, adenosine is quickly released during ischemia and exerts potent coronary vasodilatation to maintain coronary blood flow through A2 receptors. This adenosine-induced coronary vasodilatation could be coupled with KATP channels based on the evidence of the augmentation effect of KCOs. Nitric oxide may also play some role in both first and second window of myocardial protection. It is possible that rapid and reversible phosphorylation and activation of constitutive expressed myocardial NOS or by direct KATP channel phosphorylation and activation leads to the first window of myocardial protection. This hypothesis can be further investigated either by using site direct mutagenesis of iNOS or KATP channel, or by applying the dominant negative iNOS in the cell ischemic model, or by building the adenosine or iNOS knock-out mice to study the relationship of these possible mechanisms. Recently, Kontos further showed that KCOs need L-lysine or L-arginine to dilate cerebral arterioles. This suggests that there may be an amino acid binding site inside the KATP channel and nitric oxide can open the KATP channel either by direct acting on the channel protein or by modulating the affinity of the amino acid binding site for L-lysine or L-arginine. Other KATP channel openers in need of additional characterization are the Type III KCOs (nicorandiol). They open the KATP channel only in the presence of elevated intracellular NDPs, which may make them specifically target to the ischemic region, because the intracellular NDP increases mostly in ischemic region. It is possible that type III KCOs can selectively improve blood flow to ischemic areas without diverting blood away to non-ischemic region, and prevents the "steal phenomenon". (ABSTRACT TRUNCATED)

Author(s):
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Title:
Effect of L-arginine administration on myocardial thallium-201 perfusion during exercise in patients with angina pectoris and normal coronary angiograms [see comments]

Source:
J Nucl Cardiol (JOURNAL OF NUCLEAR CARDIOLOGY) 2000 Mar-Apr; 7 (2): 97-102

Abstract:
OBJECTIVES: We tested the hypothesis that an exogenous

supplement of L-arginine could alleviate coronary perfusion abnormality during exercise in patients with angina pectoris and normal coronary arteries. METHODS AND RESULTS: Twelve patients underwent exercise thallium-201 scintigraphy without medication (control) and after intravenous administration of L-arginine. Exercise time was prolonged in the L-arginine study compared with the control (482 s vs 540 s, P < .05). TI-201 extent score was improved in the L-arginine study (0.33 vs 0.26, P < .05), and the severity score was also improved (23.7 vs 16.9, P < .05). In 7 of the 12 patients whose TI-201 redistribution disappeared in the L-arginine study, the percent increase in serum L-citrulline concentration during exercise was larger than that of the remaining 5 patients (18% vs 0.9%, P < .01). The percent reduction in epicardial coronary diameter in response to acetylcholine was also greater in the former group (28.3% vs 11.1%, P < .05). CONCLUSION: Exogenous L-arginine improved myocardial perfusion during exercise in a subset of patients with angina pectoris and normal coronary arteries, probably by increasing production of nitric oxide.

Author(s):
Tentolouris C ; Tousoulis D ; Davies GJ ; Stefanadis C ; Toutouzas P
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Title:
Serum cholesterol level, cigarette smoking, and vasomotor responses to L-arginine in narrowed epicardial coronary arteries.

Source:
Am J Cardiol (AMERICAN JOURNAL OF CARDIOLOGY) 2000 Feb 15; 85 (4): 500-3, A11

Abstract:
We examined the impact of serum cholesterol and cigarette smoking on the coronary vasomotor effects of L-arginine in patients with atherosclerotic coronary artery disease. The dilation of proximal and distal segments in response to low-dose L-arginine was greater in patients with a serum cholesterol level < or =200 mg/dl than in patients with a level >200 mg/dl, whereas the response was the same in smokers and nonsmokers.

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Title:
Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 2000 Mar 1; 35 (3): 706-13

Abstract:
OBJECTIVES: The aim of this study was to analyze whether L-arginine (L-arg.) has comparable or additive effects to physical exercise regarding endothelium-dependent vasodilation

in patients with chronic heart failure (CHF). BACKGROUND: Endothelial dysfunction in patients with CHF can be corrected by both dietary supplementation with L-arg. and regular physical exercise. METHODS: Forty patients with severe CHF (left ventricular ejection fraction 19 +/- 9%) were randomized to an L-arg. group (8 g/day), a training group (T) with daily handgrip training, L-arg. and T (L-arg. + T) or an inactive control group (C). The mean internal radial artery diameter was determined at the beginning and after four weeks in response to brachial arterial administration of acetylcholine (ACh) (7.5, 15, 30 microg/min) and nitroglycerin (0.2 mg/min) with a transcutaneous high-resolution 10 MHz A-mode echo tracking system coupled with a Doppler device. The power of the study to detect clinically significant differences in endothelium-dependent vasodilation was 96.6%. RESULTS: At the beginning, the mean endothelium-dependent vasodilation in response to ACh, 30 microg/min was 2.54 +/- 0.09% (p = NS between groups). After four weeks, internal radial artery diameter increased by 8.8 +/- 0.9% after ACh 30 microg/min in L-arg. ($p < 0.001$ vs. C), by 8.6 +/- 0.9% in T ($p < 0.001$ vs. C) and by 12.0 +/- 0.3% in L-arg. +/- T ($p < 0.005$ vs. C, L-arg. and T). Endothelium-independent vasodilation as assessed by infusion of nitroglycerin was similar in all groups at the beginning and at the end of the study. CONCLUSIONS: Dietary supplementation of L-arg. as well as regular physical exercise improved agonist-mediated, endothelium-dependent vasodilation to a similar extent. Both interventions together seem to produce additive effects with respect to endothelium-dependent vasodilation.

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Title:
Effects of oral L-arginine on endothelium-dependent vasodilation and markers of inflammation in healthy postmenopausal women.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 2000 Feb; 35 (2): 271-6

Abstract:
OBJECTIVES: We examined whether oral administration of L-arginine, the substrate for nitric oxide (NO) synthesis, increases NO bioactivity in healthy postmenopausal women. BACKGROUND: Nitric oxide may protect arteries against atherosclerosis, as suggested by experimental studies in animals. Estrogen therapy, which has been shown to increase NO bioactivity in the vasculature of healthy postmenopausal women, is not acceptable for long-term use by many women. METHODS: In a randomized, double-blind, crossover study, 10 postmenopausal women without additional risk factors for

atherosclerosis received L-arginine 9 g or placebo daily for one month, with treatment periods separated by one month. Nitric oxide levels in serum (as an index of endothelial NO release), brachial artery endothelium-dependent dilator responses to hyperemia by ultrasonography (as an index of vascular NO bioactivity) and markers of inflammation in blood that are inhibited by NO in cell culture experiments were measured at the end of each treatment period. RESULTS: L-arginine levels in plasma were increased in all women during L-arginine treatment compared with placebo (136.8 +/- 63.1 vs. 75.2 +/- 16.2 micromol/liter, p = 0.009). However, there was no change in serum nitrogen oxide levels (42.1 +/- 24.5 vs. 39.1 +/- 16.6 micromol/liter, p = 0.61), nor was there an effect of L-arginine on flow-mediated dilation during hyperemia (3.8 +/- 3.0% vs. 4.9 +/- 4.8%, p = 0.53) compared with placebo. Our study had sufficient power (beta = 0.80) to detect a true absolute treatment difference in flow-mediated brachial artery dilation of 1.7% or larger as statistically significant at alpha = 0.05. There was no effect of L-arginine on serum levels of soluble cell adhesion molecules compared with placebo: E-selectin (50.6 +/- 14.8 vs. 52.1 +/- 17.0 ng/ml, p = 0.45), intercellular adhesion molecule-1 (230 +/- 51 vs. 230 +/- 52 ng/ml, p = 0.97) and vascular cell adhesion molecule-1 (456 +/- 62 vs. 469 +/- 91 ng/ml, p = 0.53). CONCLUSIONS: Oral administration of L-arginine may not augment endothelial NO synthesis and release in postmenopausal women and is thus unlikely to be of general benefit to healthy postmenopausal women in protection from the development of atherosclerosis.

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Title:
Nitric oxide effects on myocardial functionand force-interval relations: regulation of twitch duration.

Source:
J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1999 Dec; 31 (12): 2077-85

Abstract:
As the precise role of nitric oxide (NO) as a modulator of myocardial contraction and the force-interval relationship remains unclear, the objective of this study was to examine the effect of the NO donor S-nitroso-N-acetyl-penicillamine (SNAP) on baseline myocardial contraction, and the impact of both SNAP and the NO synthase (NOS) inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME) on the force interval relation. Studies were performed using isolated rat papillary muscles. In the presence of baseline NOS blockade, nanomolar to micromolar concentrations of SNAP exerted a modest positive inotropic effect with a small but significant increase in twitch isometric tension (P<0.007). Nanomolar

concentrations of SNAP also reduced overall twitch duration (P<0.007). These effects were not seen in control experiments using N-acetyl-penicillamine instead of SNAP. The force-frequency response (FFR) and post-rest contractile potentiation, mechanical correlates of sarcoplasmic reticulum (SR) Ca(2+)handling, were also examined. Neither L-NAME nor SNAP had any effect on post-rest potentiation following rest intervals as long as 6 min, or on the negative FFR at stimulation frequencies between 0.3 to 1.7 Hz. However, L-NAME significantly blunted the net reduction in twitch duration between 0.3 Hz and 1.7 Hz compared to control (P=0.006), an effect reversed by 100 n m SNAP. These results indicate that low concentrations of NO can modulate myocardial function by influencing myocardial inotropy and the time course of myofilament interaction, but do not impact significantly on the force-interval relation and, by inference, SR Ca(2+)handling. Moreover, modulation of twitch duration occurs over a range of stimulation frequencies, suggesting a mechanistic role for NO in the changes in contraction and relaxation time intervals seen during changes in heart rate. Copyright 1999 Academic Press.

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Title:
Gene transfer of nitric oxide synthase: effects on endothelial biology.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1999 Oct; 34 (4): 1201-7

Abstract:
OBJECTIVES: The purpose of the study was to investigate the role of nitric oxide (NO) in monocyte-endothelial interaction by augmenting NO release via transfection of human endothelial cells (ECs) with EC NO synthase (eNOS) DNA. BACKGROUND: Enhancement of NO synthesis by L-arginine or shear stress reduces endothelial adhesiveness for monocytes and inhibits atherogenesis. To elucidate further the underlying mechanism, we augmented NO synthase expression by transfection of human EC. METHODS: Liposome-mediated transfection of EC was performed with a plasmid construct containing the gene encoding eNOS. Expression of eNOS was confirmed by reverse transcription-polymerase chain reaction (RT-PCR). Endothelial cells were exposed to human monocytoid cells, and adherent cells were quantitated using a computer-assisted program. Nitric oxide was measured by chemiluminescence. RESULTS: The NO levels were not different in EC that were either not transfected, transfected with beta-gal or liposomes only. The nitric oxide synthase (NOS) transfection increased NO release by +60% (n = 6), which increased further when EC were stimulated by shear stress (24 h) by +137% (n = 5) as compared with untransfected, unstimulated EC (both p < 0.05). The RT-PCR revealed diminished monocyte chemotactic protein-1 (MCP-1)

expression in eNOS transfected EC. There was an inverse relation between NO levels and monocyte binding ($r = -0.5669$, $p < 0.002$). Stimulation of EC with tumor necrosis factor-alpha (TNF-alpha; 250 U/ml) led to a decrease in NO synthesis, and an increase in monocyte binding. Cells transfected with NOS were resistant to both effects of TNF-alpha. CONCLUSIONS: Endothelial cells transfected with eNOS synthesize an increased amount of NO; this is associated with diminished MCP-1 expression and monocyte-endothelial binding. The reduction in monocyte-endothelial binding persists even after cytokine stimulation.

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Title:
Treatment of the hypertensive patient with microvascular angina.

Source:
Curr Opin Cardiol (CURRENT OPINION IN CARDIOLOGY) 1999 Sep; 14 (5): 370-4

Abstract:
Syndrome X and microvascular angina are a heterogenous group of diseases. Several medications, including angiotensin-converting enzyme inhibitors, beta-blockers, and calcium-channel blockers, have been reported to be successful in the treatment of microvascular angina. Control of hypertension and regression of left ventricular hypertrophy are important in controlling symptoms associated with this intriguing problem. The role of nitric oxide and the effects of L-arginine in the pathogenesis and treatment of hypertension and microvascular angina need to be elucidated. Optimal treatment will depend on the appropriate classification and diagnosis of chest pain in patients with hypertension and normal coronary angiograms.

Author(s):
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Title:
Non-anticoagulant heparin increases endothelial nitric oxide synthase activity: role of inhibitory guanine nucleotide proteins.

Source:
J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1998 Dec; 30 (12): 2669-82

Abstract:
Heparin, which is widely used clinically, has recently been shown to have specific properties affecting the vascular endothelium. We hypothesized that heparin stimulates endothelial nitric oxide synthase (eNOS) activity by a mechanism independent of its anticoagulant properties and dependent on an inhibitory guanine nucleotide regulatory protein (Gi). We

determined the effect of both heparin and N-acetyl heparin (Non-Hep), a heparin derivative without anticoagulant properties, on eNOS activity in cultured bovine aortic endothelial cells and on endothelium-dependent relaxation in isolated vascular rings. The eNOS activity was determined by measuring both citrulline and nitric oxide (NO) metabolite formation. Heparin and Non-Hep dose-dependently increased basal eNOS activity (ED50 1.0 microgram/ml or 0.15 U/ml), an effect that was significantly inhibited by pertussis toxin (100 ng/ml), a Gi-protein inhibitor. Agonist-stimulated (acetylcholine, 10 microM) eNOS activity was potentiated following pre-treatment with both heparin and Non-Hep and reversed by pertussis toxin. Heparin and Non-Hep induced a dose-dependent relaxation in preconstricted thoracic aortic rings, an effect that was significantly inhibited by pertussis toxin, endothelial inactivation (following treatment with sodium deoxycholate) and NG-nitro-L-arginine-methyl ester (L-NAME). We conclude that heparin and non-anticoagulant heparin induce endothelium-dependent relaxation following activation of eNOS by a mechanism involving a Gi-protein. Administration of heparin derivatives without anticoagulant properties may have therapeutic implications for the preservation of eNOS in conditions characterized by endothelial dysfunction.

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Title:
Neurohormonal activation in the treatment of congestive heart failure: basis for new treatments?

Source:
Cardiology (CARDIOLOGY) 1998 Jul; 90 (1): 1-7

Abstract:
Traditionally, the pathophysiology of heart failure was viewed as a derangement in hemodynamic factors. Impairment in cardiac function resulted in decreased cardiac output and end-organ hypoperfusion triggering compensatory increases in heart rate, blood pressure and cardiac contractility. While initially beneficial, these mechanisms placed additional stress on the failing heart. Unfortunately, pharmacologic therapies that restored hemodynamic balance failed to halt disease progression. The activation of neurohormonal responses, including those of the renin-angiotensin-aldosterone system, the sympathetic nervous system and the arginine vasopressin system, has been implicated in the progression of heart disease. In acute heart failure, their effects help to restore cardiovascular homeostasis. However, the chronic stimulation of these systems eventually leads to worsening left ventricular function. Drug treatments that activate neurohormonal systems may have long-term clinically deleterious outcomes, and therefore new pharmacological therapies for cardiovascular disease must take into account the interaction between neurohormonal activation and hemodynamic

factors.

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Title:
Role of nitric oxide in restenosis after experimental balloon angioplasty in the hypercholesterolemic rabbit: effects on neointimal hyperplasia and vascular remodeling.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1999 Mar; 33 (3): 876-82

Abstract:
OBJECTIVES: The purpose of this study was to assess the effects of L-arginine and N(G)-nitro-L-arginine methyl ester (L-NAME) on neointimal hyperplasia and vascular remodeling after balloon angioplasty in the hypercholesterolemic rabbit. BACKGROUND: Restenosis after balloon angioplasty is a consequence of both neointimal hyperplasia and vessel remodeling. Nitric oxide inhibits neointimal hyperplasia, but its effect on vessel remodeling is unknown. METHODS: Six weeks after induction of bilateral iliac atherosclerosis, 48 rabbits underwent successful angioplasty in 75 vessels. Eight rabbits (acute group) were sacrificed immediately after angioplasty. The remaining animals received either placebo (chronic control group), or a diet supplemented with either L-arginine (1.5 g/kg/day), or L-NAME (15 mg/kg/day) for 4 weeks after angioplasty. RESULTS: The intimal area was significantly greater in the chronic control group compared to the acute group (2.60+/-1.03 mm2 vs. 1.35+/-0.62 mm2). This increase in intimal area was lower in the L-arginine group (1.79+/-0.61 mm2), and greater in the L-NAME group (3.23+/-0.92 mm2). The area circumscribed by the internal elastic lamina (IEL) increased significantly in the control group compared to the acute group (from 2.52+/-0.66 to 3.33+/-0.85 mm2); a more marked increase occurred in the L-NAME group (3.90+/-0.85 mm2). By contrast, IEL area was unchanged in the L-arginine group (2.41+/-0.62 mm2). As a result, there was no significant difference in lumen area after 4 weeks in the chronic groups (control: 0.74+/-0.38 mm2; L-arginine: 0.50+/-0.43 mm2; L-NAME: 0.48+/-0.42 mm2). CONCLUSIONS: Our results demonstrate that L-arginine inhibits whereas L-NAME stimulates neointimal hyperplasia after experimental balloon angioplasty in the hypercholesterolemic rabbit. However, the lack of vessel enlargement in the L-arginine group resulted in a similar final lumen size in the L-NAME and L-arginine groups.

Author(s):
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Address: Charles A. Dana Research Institute, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical

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Title:

Chronic L-arginine treatment increases cardiac cyclic guanosine 5'-monophosphate in rats with aortic stenosis: effects on left ventricular mass and beta-adrenergic contractile reserve.

Source:

J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Aug; 32 (2): 528-35

Abstract:

OBJECTIVES: We tested the hypothesis that nitric oxide (NO) cyclic guanosine 5'-monophosphate (GMP) signaling is deficient in pressure overload hypertrophy due to ascending aortic stenosis, and that long-term L-arginine treatment will increase cardiac cyclic GMP production and modify left ventricular (LV) pressure overload hypertrophy and beta-adrenergic contractile response. BACKGROUND: Nitric oxide cyclic GMP signaling is postulated to depress vascular growth, but its effects on cardiac hypertrophic growth are controversial. METHODS: Forty control rats and 40 rats with aortic stenosis left ventricular hypertrophy ([LVH] group) were randomized to receive either L-arginine (0.40 g/kg/day) or no drug for 6 weeks. RESULTS: The dose of L-arginine did not alter systemic blood pressure. Animals with LVH had similar LV constitutive nitric oxide synthase (cNOS) mRNA and protein levels, and LV cyclic GMP levels as compared with age-matched controls. In rats with LVH L-arginine treatment led to a 35% increase in cNOS protein levels ($p = 0.09$ vs untreated animals with LVH) and a 1.7-fold increase in LV cyclic GMP levels ($p < 0.05$ vs untreated animals with LVH). However, L-arginine treatment did not suppress LVH in the animals with aortic stenosis. In contrast, in vivo LV systolic pressure was depressed in L-arginine treated versus untreated rats with LVH (163 +/- 16 vs 198 +/- 10 mm Hg, $p < 0.05$). In addition, the contractile response to isoproterenol was blunted in both isolated intact hearts and isolated myocytes from L-arginine treated rats with LVH compared with untreated rats with LVH. This effect was mediated by a blunted increase in peak systolic intracellular calcium in response to beta-adrenergic stimulation. CONCLUSIONS: Left ventricular hypertrophy due to chronic mechanical systolic pressure overload is not characterized by a deficiency of LV cNOS and cyclic GMP levels. In rats with aortic stenosis, L-arginine treatment increased cardiac levels of cyclic GMP, but it did not modify cardiac mass in rats with aortic stenosis. However, long-term stimulation of NO-cyclic GMP signaling depressed in vivo LV systolic function in LVH rats and markedly blunted the contractile response to beta-adrenergic stimulation.

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Title:

Nut consumption, lipids, and risk of a coronary event.

Source:

Clin Cardiol (CLINICAL CARDIOLOGY) 1999 Jul; 22 (7 Suppl): III11-5 Journal Code: DE9

Abstract:

In the past, many have avoided nuts because of their high fat content. The Dietary Approaches to Stop Hypertension (DASH) diet, however, recommends regular consumption of this food along with seeds and dried beans (4-5 servings per week) as part of a diet to control hypertension. Nuts are nutrient-dense and most of their fat is unsaturated. They are also perhaps the best natural source of vitamin E and are relatively concentrated repositories of dietary fiber, magnesium, potassium, and arginine, the dietary precursor of nitric oxide. Human feeding studies have demonstrated reductions of 8-12% in low-density lipoprotein (LDL) cholesterol when almonds and walnuts are substituted for more traditional fats. Other studies show that macadamias and hazelnuts appear at least as beneficial as fats in commonly recommended diets. Whether consuming modest quantities of nuts daily may promote weight gain is not known with certainty, but preliminary data suggest that this is unlikely. Four of the best and largest cohort studies in nutritional epidemiology have now reported that eating nuts frequently is associated with a decreased risk of coronary heart disease of the order of 30-50%. The findings are very consistent in subgroup analyses and unlikely to be due to confounding. Possible mechanisms include reduction in LDL cholesterol, the antioxidant actions of vitamin E, and the effects on the endothelium and platelet function of higher levels of nitric oxide. Although nuts may account for a relatively small percentage of dietary calories, the potential interacting effects of these factors on disease risk may be considerable.

Author(s):

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Title:

Familial hypertrophic cardiomyopathy associated with a novel missense mutation affecting the ATP-binding region of the cardiac beta-myosin heavy chain.

Source:

J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1999 Apr; 31 (4): 745-50 Journal Code: J72

Abstract:

Mutations in the cardiac beta -myosin heavy chain gene (MYH7), and other genes encoding cardiac sarcomere proteins may cause familial hypertrophic cardiomyopathy (F-HCM), an autosomal dominant disease, characterized by myocardial hypertrophy. We analysed the MYH7 gene in three generations of a family with one borderline and four clinically verified cases of hypertrophic cardiomyopathy, and identified a mutation in exon 7 changing the 190 arginine residue into a threonine residue. The mutation is located in the ATP-binding region of the myosin head and alters

the charge in the F-helix close to the phosphate-binding P-loop. The mutation may thus interfere with the coupling between ATP-hydrolysis and the transition into mechanical energy. In conclusion, the novel Arg190Thr mutation in exon 7 of the MYH7 gene is associated with the development of symptomatic myocardial hypertrophy in adults. Copyright 1999 Academic Press.

Author(s):
Blum A ; Porat R ; Rosenschein U ; Keren G ; Roth A ; Laniado S ; Miller H
Address: Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA.
Title:
Clinical and inflammatory effects of dietary L-arginine in patients with intractable angina pectoris.
Source:
Am J Cardiol (AMERICAN JOURNAL OF CARDIOLOGY) 1999 May 15; 83 (10): 1488-90, A8 Journal Code: 3DQ
Additional Info: UNITED STATES
Abstract:
We evaluated the effects of oral L-arginine on the clinical outcome and the inflammatory markers of patients with intractable angina pectoris. Our findings demonstrated a significant clinical improvement in 7 of 10 patients, which was associated with a significant decrease in cell adhesion molecule and proinflammatory cytokine levels. Dietary L-arginine may have clinical beneficial effects in patients with intractable angina pectoris, and may have anti-inflammatory properties.

Author(s):
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Address: Medizinische Hochschule Hannover, Germany.
Title:
Endothelial dysfunction in human disease.
Source:
J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1999 Jan; 31 (1): 51-60 Journal Code: J72
Additional Info: ENGLAND
Abstract:
The vascular endothelium plays a key role in the local regulation of vascular tone by the release of vasodilator substances (i.e. endothelium-derived relaxing factor (EDRF = nitric oxide, NO) and prostacyclin) and vasoconstrictor substances (i.e. thromboxane A2, free radicals, or endothelin). Using either agents like acetylcholine or changes in flow to stimulate the release of EDRF (NO), clinical studies have revealed the importance of EDRF in both basal and stimulated control of vascular tone in large epicardial coronary arteries and in the coronary microcirculation. The regulatory function of the endothelium is altered by cardiovascular risk factors or disorders such as hypercholesterolemia, chronic smoking, hypertension or chronic heart failure. Endothelial dysfunction

appears to have detrimental functional consequences as well as adverse longterm effects, including vascular remodelling. Endothelial dysfunction is associated with impaired tissue perfusion particularly during stress and paradoxical vasoconstriction of large conduit vessels including the coronary arteries. These effects may cause or contribute to myocardial ischemia. Several mechanisms may be involved in the development of endothelial dysfunction, such as reduced synthesis and release of EDRF or enhanced inactivation of EDRF after its release from endothelial cells by radicals or oxidized low-density lipoprotein (LDL). Increased plasma levels of oxidized LDL have been noted in chronic smokers and are related to the extent endothelial dysfunction, raising the possibility that chronic smoking potentiates endothelial dysfunction by increasing circulating and tissue levels of oxidized LDL. In heart failure, cytokines and/or reduced flow (reflecting reduced shear stress) may be involved in the development of endothelial dysfunction and can be reversed by physical training. Other mechanisms include an activated renin-angiotensin system (i.e. postmyocardial infarction) with increased breakdown of bradykinin by enhanced angiotensin converting enzyme (ACE) activity. There is evidence that endogenous bradykinin is involved in coronary vasomotor control both in coronary conduit and resistance vessels. ACE inhibitors enhance endothelial function by a bradykinin-dependent mechanism and probably also by blunting the generation of superoxide anion. Endothelial dysfunction appears to be reversible by administering L-arginine, the precursor of nitric oxide, lowering cholesterol levels, physical training, antioxidants such as vitamin C, or ACE inhibition.

Author(s):
Fleming I ; Busse R
Address: Institut für Kardiovaskuläre Physiologie, Klinikum der J.W. Goethe-Universität, Frankfurt am Main, Germany.
Title:
NO: the primary EDRF.
Source:
J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1999 Jan; 31 (1): 5-14 Journal Code: J72
Additional Info: ENGLAND
Abstract:
Since the discovery of an endothelium-derived relaxing factor (EDRF) by Furchgott and Zawadzki (Furchgott and Zawadzki. 1980), which was later identified as nitric oxide (NO) (Ignarro et al., 1987; Palmer et al., 1987; Furchgott, 1988), it has become clear that there are a number of additional endothelium-derived vasodilator and vasoconstrictor autacoids (endothelin-1, prostaglandin H2, and the endothelium-derived hyperpolarizing factor: EDHF). None of these autacoids play such a central role in the regulation of vascular tone and homeostasis as the primary EDRF, the free radical NO, which is generated via a live-electron oxidation of a guanidino nitrogen from L-arginine

by an NO synthase (NOS).

Author(s):
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Title:
Secondary endothelial dysfunction:hypertension and heart failure.
Source:
J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1999 Jan; 31 (1): 39-49 Journal Code: J72
Additional Info: ENGLAND
Abstract:
The endothelium is a major regulator of vascular tone, releasing vasoactive substances such as endothelium-derived nitric oxide (EDRF), endothelium-derived hyperpolarizing factor(s), cycloxygenase metabolites, endothelin and other endothelium-derived contracting factors (EDCF). In a number of cardiovascular pathologies, such as hypertension or heart failure, the balance in the endothelial production of vasodilating and vasoconstricting mediators is altered. The resulting apparent decrease in endothelium-dependent relaxations is termed 'endothelial dysfunction'. In hypertensive patients and in animal models of hypertension, endothelium-dependent relaxations are impaired. However, this endothelial dysfunction presents different characteristics depending on the model studied. In Dahl-salt-sensitive rats, the decrease in endothelium-dependent relaxations is associated with impaired constitutive nitric oxide synthase activity. The presence of an endogenous nitric oxide synthase inhibitor and a decreased response of vascular smooth muscle to the mediator may contribute also to the dysfunction observed in this model. In other animal models of hypertension (such as spontaneous hypertension). the contribution of the L-arginine nitric oxide pathway to endothelium-dependent responses appears normal or impaired despite reports of increased nitric oxide synthase activity or expression. In large arteries from SHR, endothelium-dependent relaxations are impaired mainly because of the concomitant augmented release of endoperoxides activating thromboxane-endoperoxide receptors. Superoxide anions may also play a role in some models, but only in the early phase of the disease: whether or not these species contribute to further development of endothelial dysfunction or to increases in blood pressure remains to be examined. The endothelial dysfunction observed in hypertension is likely to be a consequence of high blood pressure. but it could facilitate the maintenance of elevated peripheral resistance at a later stage in the disease and favour the occurrence of complications, such as atherosclerosis.

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Title:

Primary endothelial dysfunction: atherosclerosis.

Source:

J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1999 Jan; 31 (1): 23-37 Journal Code: J72

Abstract:

The endothelium synthesizes and releases several vasodilating factors, including nitric oxide, endothelium-derived hyperpolarizing factor, and prostacyclin. Under certain conditions, it also liberates vasocontracting factors. Thus, the endothelium plays an important role in regulating vascular homeostasis. Several intracellular mechanisms are involved in the synthesis of nitric oxide, including receptor-coupled G proteins, the availability of L-arginine, cofactors for endothelial nitric oxide synthase and the expression of the enzyme. Endothelial dysfunction by aging, menopause and hypercholesterolemia is involved in the development of atherosclerotic vascular lesions, and predisposes the blood vessel to several vascular disorders, such as vasospasm and thrombosis. Multiple mechanisms are apparently involved in the pathogenesis of the endothelial dysfunction in atherosclerosis. The reduced production of nitric oxide by the endothelium is caused by abnormalities in endothelial signal transduction, availability of L-arginine, cofactors for endothelial nitric oxide synthase and expression of the enzyme. Other mechanisms may also be involved in the impaired endothelium-dependent relaxations in atherosclerosis, including increased destruction of nitric oxide by superoxide anion, altered responsiveness of vascular smooth muscle, and concomitant release of vasocontracting factors. In addition to the treatment of the underlying risk factors, several pharmacological agents can improve endothelial dysfunction in atherosclerosis. Thus, the endothelium is a novel therapeutic target for the treatment of atherosclerotic cardiovascular disease.

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Title:

Nitric oxide synthase in experimental autoimmune myocarditis dysfunction.

Source:

J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1998 Nov; 30 (11): 2467-74

Abstract:

This study reports the expression of inducible nitric oxide synthase (NOS) in heart from autoimmune myocarditis mice associated with an alteration in their contractile behavior. By mean of the production of [U-14C]citrulline from [U-14C]arginine and immunoblot assay, the expression of iNOS

was demonstrated in autoimmune atria that was normally absent. The iNOS activity decreased with administration of dexamethasone and in mice treated with monoclonal anti-interferon-gamma antibody (anti-IFN-gamma mAb). The inhibitors of protein kinase C activity (staurosporine) but not calcium/calmodulin (trifluoperazine) attenuated the iNOS activity. Moreover, autoimmune atria presented contractile alterations (lower values of dF/dt than control). The in vivo treatment with inhibitors of NOS activity or anti-IFN-gamma mAb or dexamethasone improved the contractile activity of autoimmune atria with no change in the contractility of normal atria. The results suggest that the infiltrative cells in myocarditis heart have a potential role in cardiac dysfunction by production of IFN-gamma and subsequent expression of iNOS, that in turn alter the contractile behavior of the heart. The data indicate that cytokines induced activation of L-arginine nitric oxide pathway in myocarditis atria leading to contractile dysfunction.

Author(s):
Tenenbaum A ; Fisman EZ ; Motro M
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Title:
L-Arginine: rediscovery in progress.
Source:
Cardiology (CARDIOLOGY) 1998 Dec; 90 (3): 153-9
Journal Code: COI
Additional Info: SWITZERLAND
Standard No:
ISSN: 0008-6312
Language:
ENGLISH
Abstract:
Since the recognition that L-arginine (LA) is the natural metabolic donor of nitric oxide, this amino acid has reached the medical spotlight. LA exerts favorable effects in the prevention and treatment of endothelial damage and the restoration of endothelial function in patients with cardiovascular risk factors (hypercholesterolemia, smoking, hypertension, diabetes and advanced age) or with several chronic cardiovascular disorders (coronary, peripheral and cerebral vascular disease, and mild-to-moderate heart failure). LA administration is likely to represent a potentially novel therapeutic strategy during angioplasty, coronary bypass grafting and cardiac transplantation. More conclusive research findings for the rediscovered role of this well-known substance merit close attention.

Author(s):
Cooke JP

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Title:
Nutriceuticals for cardiovascular health.

Source:
Am J Cardiol (AMERICAN JOURNAL OF CARDIOLOGY) 1998 Nov 19; 82 (10A): 43S-46S Journal Code: 3DQ
Additional Info: UNITED STATES

Standard No:
ISSN: 0002-9149

Language:
ENGLISH

References:
Number: 29

MESH Subject(s) below:

Descriptor:
Antioxidants -- Therapeutic Use
Arginine -- Therapeutic Use
Cardiovascular Diseases -- Drug Therapy
Flavones -- Therapeutic Use
Dietary Supplements
Middle Age
Female
Human
Male

Chemical Subst:
0 (Antioxidants)
0 (Flavones)
7004-12-8 (Arginine)

Author(s):
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Title:
The role of adenosine and ATP-sensitive potassium channels in the protection afforded by ischemic preconditioning against the post-ischemic endothelial dysfunction in guinea-pig hearts.

Source:
J Mol Cell Cardiol (JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY) 1998 Sep; 30 (9): 1735-47 Journal Code: J72

Abstract:
The role of adenosine and ATP-sensitive potassium channels (KATP) in the mechanism of ischemic preconditioning (IPC)-induced protection against the post-ischemic endothelial dysfunction was studied. Langendorff-perfused guinea-pig hearts were subjected either to 40 min of global ischemia and 40 min reperfusion or were preconditioned prior to the ischemia/reperfusion with three cycles of either 5 min ischemia/5 min reperfusion (IPC) or 5 min infusion/5 min wash-out of adenosine, adenosine A1 receptor agonist, N6-cyclohexyladenosine (CHA) or KATP opener, pinacidil. The

magnitude of coronary flow reduction caused by NO-synthase inhibitor, Nomega-nitro-l-arginine methyl ester (l-NAME), served as an index of a basal endothelium-dependent vasodilator tone. Coronary overflows produced by a bolus of acetylcholine (ACh) and sodium nitroprusside (SNP) were used as measures of agonist-induced endothelium-dependent and endothelium-independent vascular function, respectively. The coronary flow, LVDP, ACh response and l-NAME response were reduced by 8, 32, 41 and 54%, respectively, while SNP response was not changed in the hearts subjected to ischemia/reperfusion. ACh response was fully restored, l-NAME response was partially restored, and SNP response was not affected in the hearts subjected to IPC. The post-ischemic recoveries of coronary flow and LVDP were not improved by IPC. The protective effect of IPC on the ACh response was mimicked by adenosine, CHA, and pinacidil. The protective effect of IPC, CHA and pinacidil was abolished by KATP antagonist, glibenclamide. The IPC protection was affected neither by a non-specific adenosine antagonist, 8-p-sulfophenyltheophylline, nor by a specific adenosine A1 receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX). Our data indicate that: (1) IPC affords endothelial protection in the mechanism that involves activation of KATP, but not adenosine A1 receptors; (2) exogenous adenosine and A1 receptor agonist afford the protection, which might be of a potential clinical significance; (3) the endothelial dysfunction is not involved in the mechanism of myocardial stunning in guinea-pig hearts. Copyright 1998 Academic Press.

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Title:
Restoring vascular nitric oxide formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Nov; 32 (5): 1336-44 Journal Code: H50
Additional Info: UNITED STATES
Standard No:
ISSN: 0735-1097
Language:
ENGLISH

Abstract:
BACKGROUND: Administration of L-arginine improves nitric oxide (NO) formation and endothelium-dependent vasodilation in atherosclerotic patients. OBJECTIVES: We investigated in this double-blind, controlled study whether prolonged intermittent infusion therapy with L-arginine improves the clinical

symptoms of patients with intermittent claudication, as compared with the endothelium-independent vasodilator prostaglandin E1, and control patients. METHODS: Thirty-nine patients with intermittent claudication were randomly assigned to receive 2 x 8 g L-arginine/day, or 2 x 40 microg prostaglandin E1 (PGE1)/day or no hemodynamically active treatment, for 3 weeks. The pain-free and absolute walking distances were assessed on a walking treadmill at 3 km/h, 12% slope, and NO-mediated, flow-induced vasodilation of the femoral artery was assessed by ultrasonography at baseline, at 1, 2 and 3 weeks of therapy and 6 weeks after the end of treatment. Urinary nitrate and cyclic guanosine-3', 5'-monophosphate (GMP) were assessed as indices of endogenous NO production. RESULTS: L-Arginine improved the pain-free walking distance by 230+/-63% and the absolute walking distance by 155+/-48% (each $p < 0.05$). Prostaglandin E1 improved both parameters by 209+/-63% and 144+/-28%, respectively (each $p < 0.05$), whereas control patients experienced no significant change. L-Arginine therapy also improved endothelium-dependent vasodilation in the femoral artery, whereas PGE1 had no such effect. There was a significant linear correlation between the L-arginine/asymmetric dimethylarginine (ADMA) ratio and the pain-free walking distance at baseline ($r=0.359$, $p < 0.03$). L-Arginine treatment elevated the plasma L-arginine/ADMA ratio and increased urinary nitrate and cyclic GMP excretion rates, indicating normalized endogenous NO formation. Prostaglandin E1 therapy had no significant effect on any of these parameters. Symptom scores assessed on a visual analog scale increased from 3.51+/-0.18 to 83+/-0.4 (L-arginine) and 7.0+/-0.5 (PGE1; each $p < 0.05$), but did not significantly change in the control group (4.3+/-0.4). CONCLUSIONS: Restoring NO formation and endothelium-dependent vasodilation by L-arginine improves the clinical symptoms of intermittent claudication in patients with peripheral arterial occlusive disease.

Author(s):
Cardillo C ; Kilcoyne CM ; Cannon RO 3rd ; Panza JA
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Title:
Impairment of the nitric oxide-mediated vasodilator response to mental stress in hypertensive but not in hypercholesterolemicpatients.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Nov; 32 (5): 1207-13 Journal Code: H50

Abstract:
OBJECTIVES: This study investigated whether mental stress-induced vasodilation mediated by endothelium-derived nitric oxide (NO) is defective in conditions with endothelial dysfunction, such as hypertension and hypercholesterolemia.

BACKGROUND: Vascular release of NO modulates the vasodilator response to mental stress in healthy subjects. Previous studies have shown that hypertensive and hypercholesterolemic patients have impaired endothelium-dependent vasodilation to pharmacologic agents due to decreased NO activity. However, whether this abnormality also operates in response to physiologic stimuli such as mental stress has not been defined. METHODS: Forearm blood flow responses (plethysmography) to mental stress were compared in 12 normal subjects, 12 hypertensive patients and 10 hypercholesterolemic patients before and during NO synthesis inhibition with N(G)-monomethyl-L-arginine (4 micromol/min). Vascular responses to acetylcholine (7.5, 15 and 30 microg/min), an endothelium-dependent vasodilator, and sodium nitroprusside (0.8, 1.6 and 3.2 microg/min), an exogenous NO donor, were also assessed in each group. RESULTS: During saline the vasodilator response to mental stress was significantly blunted in hypertensive (37+/-11%; p=0.01) but not in hypercholesterolemic (85+/-21%; p=0.78) patients compared with controls (93+/-15%). N(G)-Monomethyl-L-arginine administration significantly blunted mental stress-induced vasodilation in healthy subjects (p=0.004 vs. saline) and hypercholesterolemic patients (p=0.03 vs. saline), but not in hypertensive patients (p=0.69 vs. saline). The vasodilator effect of the highest dose of acetylcholine was similarly blunted in hypertensive (215+/-44%; p=0.02) and hypercholesterolemic (172+/-71%; p=0.02) patients compared with controls (364+/-34), whereas the vasorelaxing response to sodium nitroprusside was similar in the three groups. CONCLUSIONS: Hypertensive but not hypercholesterolemic patients have impaired NO-dependent vasodilation during mental stress. These findings may be accounted for by different mechanisms underlying endothelial dysfunction in these two conditions and might explain an increased susceptibility of hypertensive patients to vascular damage over repeated exposure to stressful situations.

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Title:
Expression, activity and functional significance of inducible nitric oxide synthase in the failing human heart.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Oct; 32 (4): 955-63 Journal Code: H50

Abstract:
OBJECTIVES: The study was designed to evaluate the functional impact of nitric oxide (NO) generation within the myocardium on cardiac contraction in the failing human heart. BACKGROUND: Heart failure is associated with activation of cytokines and

expression of inducible nitric oxide synthase (NOS II), which generates NO from L-arginine. Nitric oxide has been shown to modulate myocardial performance, raising the possibility that cardiac generation of NO by NOS II modulates cardiac contraction in the failing human heart. METHODS: Left ventricular (LV) tissue of 24 patients with end-stage heart failure was obtained during cardiac transplantation. Gene expression of NOS II and endothelial NO-synthase (NOS III) was quantified by competitive reverse transcription-polymerase chain reaction and compared to tissues of five nonfailing donor hearts. Nitric oxide synthase II activity was determined by citrulline assay and related to changes in force of contraction induced by the beta-adrenergic agonist isoproterenol, NO-donors and/or N-mono-methyl-L-arginine (L-NMMA), an inhibitor of NOS. RESULTS: While NOS III mRNA was reduced in failing hearts, NOS II mRNA was increased in failing LV tissue and correlated with NOS II activity. High NOS II activity was associated with early relaxation and impaired responsiveness to beta-adrenergic stimulation, that is, the inotropic response to isoproterenol in failing hearts was inversely related to NOS II activity ($r=0.61$, $p < 0.005$). Nitric oxide donors or L-NMMA did not affect myocardial performance in failing hearts at baseline. However, L-NMMA enhanced the positive inotropic response to beta-adrenergic stimulation in failing hearts with high NOS II activity. Nitric oxide donors attenuated the isoproterenol-induced increase in force of contraction of failing hearts. CONCLUSIONS: Cardiac production of NO by NOS II attenuates the positive inotropic effects of beta-adrenergic stimulation and hastens relaxation in failing human hearts.

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Title:
Does acute improvement of endothelial dysfunction in coronary artery disease improve myocardial ischemia? A double-blindcomparison of parenteral D- and L-arginine.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Oct; 32 (4): 904-11 Journal Code: H50

Abstract:
OBJECTIVES: Parenteral L-arginine will improve myocardial ischemia in patients with obstructive coronary artery disease. BACKGROUND: Endothelial dysfunction causes coronary arterial constriction during stress, and L-arginine improves endothelial dysfunction. METHODS: Twenty-two patients with stable coronary artery disease and exercise-induced ST-segment depression underwent assessment of forearm endothelial function with acetylcholine and symptom-limited treadmill exercise testing during dextrose 5% infusion and after double-blind intravenous administration of L- and D-arginine (5

mg/kg/min) for 20 min. RESULTS: Forearm blood flow increased with both L- and D-arginine (33%+/-6% and 38%+/-7%, respectively, $p < 0.001$). Acetylcholine-mediated forearm vasodilation also improved with both L- and D-arginine ($p < 0.0001$). The magnitude of improvement was similar with both enantiomers and was observed in patients throughout the range of acetylcholine responses and cholesterol levels. Heart rate and blood pressure at rest and during each stage of exercise and exercise duration remained unchanged with L- and D-arginine compared to control. Ischemic threshold, measured either as the rate-pressure product or the duration of exercise at the onset of 1-mm ST-segment depression during exercise, also remained unchanged. Serum arginine, insulin and prolactin levels ($p < 0.01$) increased with both enantiomers. CONCLUSIONS: Parenteral arginine produces non-stereo-specific peripheral vasodilation and improves endothelium-dependent vasodilation in patients with stable coronary artery disease by stimulation of insulin-dependent nitric oxide release or by nonenzymatic nitric oxide generation. Despite enhanced endothelial function, there was no improvement in myocardial ischemia during stress with either enantiomer. Whether parenteral arginine will be of therapeutic benefit in acute coronary syndromes and oral arginine in myocardial ischemia needs to be studied further.

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Title:
Neurohormonal activation in the treatment of congestive heart failure: basis for new treatments?

Source:
Cardiology (CARDIOLOGY) 1998 Jul; 90 (1): 1-7 Journal Code: COI

Abstract:
Traditionally, the pathophysiology of heart failure was viewed as a derangement in hemodynamic factors. Impairment in cardiac function resulted in decreased cardiac output and end-organ hypoperfusion triggering compensatory increases in heart rate, blood pressure and cardiac contractility. While initially beneficial, these mechanisms placed additional stress on the failing heart. Unfortunately, pharmacologic therapies that restored hemodynamic balance failed to halt disease progression. The activation of neurohormonal responses, including those of the renin-angiotensin-aldosterone system, the sympathetic nervous system and the arginine vasopressin system, has been implicated in the progression of heart disease. In acute heart failure, their effects help to restore cardiovascular homeostasis. However, the chronic stimulation of these systems eventually leads to worsening left ventricular function. Drug treatments that activate neurohormonal systems may have long-term clinically deleterious outcomes, and therefore new pharmacological therapies for cardiovascular disease must take into account the

interaction between neurohormonal activation and hemodynamic factors.

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Title:
Chronic L-arginine treatment increases cardiac cyclic guanosine 5' monophosphate in rats with aortic stenosis: effects on leftventricular mass and beta-adrenergic contractile reserve.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Aug; 32 (2): 528-35 Journal Code: H50

Abstract:
OBJECTIVES: We tested the hypothesis that nitric oxide (NO) cyclic guanosine 5'-monophosphate (GMP) signaling is deficient in pressure overload hypertrophy due to ascending aortic stenosis, and that long-term L-arginine treatment will increase cardiac cyclic GMP production and modify left ventricular (LV) pressure overload hypertrophy and beta-adrenergic contractile response. BACKGROUND: Nitric oxide cyclic GMP signaling is postulated to depress vascular growth, but its effects on cardiac hypertrophic growth are controversial. METHODS: Forty control rats and 40 rats with aortic stenosis left ventricular hypertrophy ([LVH] group) were randomized to receive either L-arginine (0.40 g/kg/day) or no drug for 6 weeks. RESULTS: The dose of L-arginine did not alter systemic blood pressure. Animals with LVH had similar LV constitutive nitric oxide synthase (cNOS) mRNA and protein levels, and LV cyclic GMP levels as compared with age-matched controls. In rats with LVH L-arginine treatment led to a 35% increase in cNOS protein levels ($p = 0.09$ vs untreated animals with LVH) and a 1.7-fold increase in LV cyclic GMP levels ($p < 0.05$ vs untreated animals with LVH). However, L-arginine treatment did not suppress LVH in the animals with aortic stenosis. In contrast, in vivo LV systolic pressure was depressed in L-arginine treated versus untreated rats with LVH (163 +/- 16 vs 198 +/- 10 mm Hg, $p < 0.05$). In addition, the contractile response to isoproterenol was blunted in both isolated intact hearts and isolated myocytes from L-arginine treated rats with LVH compared with untreated rats with LVH. This effect was mediated by a blunted increase in peak systolic intracellular calcium in response to beta-adrenergic stimulation. CONCLUSIONS: Left ventricular hypertrophy due to chronic mechanical systolic pressure overload is not characterized by a deficiency of LV cNOS and cyclic GMP levels. In rats with aortic stenosis, L-arginine treatment increased cardiac levels of cyclic GMP, but it did not modify cardiac mass in rats with aortic stenosis. However, long-term stimulation of NO-cyclic GMP signaling depressed in

vivo LV systolic function in LVH rats and markedly blunted the contractile response to beta-adrenergic stimulation.

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Title:
Early endothelial dysfunction in adults at risk from atherosclerosis: different responses to L-arginine.
Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Jul; 32 (1): 110-6 Journal Code: H50
Abstract:
OBJECTIVES: We sought to examine endothelial responses to L-arginine in three groups with isolated risk factors: hypercholesterolemia, smoking and insulin-dependent diabetes mellitus (IDDM). BACKGROUND: Endothelial dysfunction occurs early in atherosclerosis, predating clinical disease. We hypothesized that the nature of endothelial injury associated with individual cardiovascular risk factors might be different and that this might affect the response to L-arginine, the substrate for endothelial nitric oxide synthase. METHODS: We studied the effects of intravenous L-arginine on brachial artery flow-mediated dilation (FMD) and glyceryl trinitrate (GTN)-mediated dilation in 36 young subjects (18 to 40 years old) without clinical atherosclerosis: 9 each of normal control subjects, hypercholesterolemic subjects, cigarette smokers and subjects with IDDM. RESULTS: Baseline FMD was significantly impaired in hypercholesterolemic subjects (mean +/- SD 1.7 +/- 2.3%), smokers (1.6 +/- 1.8%) and diabetic subjects (1.8 +/- 1.5%) compared with that in control subjects (6.9 +/- 3.3%, p = 0.001). The response to GTN was not significantly different between the subjects with risk factors and control subjects, apart from those with IDDM, in whom it was significantly impaired (p = 0.026). After infusion of L-arginine, there was no change in FMD in control or diabetic subjects. In hypercholesterolemic subjects and smokers, FMD improved from 1.9 +/- 1.9% to 4.1 +/- 2.1% (p = 0.01) and from 2.0 +/- 1.71% to 3.1 +/- 2.5% (p = 0.02), respectively. CONCLUSIONS: FMD was impaired in all three risk factor groups; however, they responded differently to L-arginine, FMD being improved in hypercholesterolemic subjects and smokers but unchanged in diabetic subjects. These results indicate differing underlying pathophysiologies that may facilitate the design of treatment strategies for subjects with different risk factors.

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Title:
Coronary vascular responsiveness toadenosine is impaired additively by blockade of nitric oxide synthesis and a sulfonylurea.

Source:
J Am Coll Cardiol (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY) 1998 Mar 15; 31 (4): 816-22 Journal Code: H50

Abstract:
OBJECTIVES: We sought to define effects of glibenclamide, a sulfonylurea known to block ATP-dependent potassium (KATP) channels, and Nomega-nitro-L-arginine methyl ester (L-NAME), an L-arginine analog known to block nitric oxide (NO) synthesis, on coronary vascular responsiveness to adenosine. BACKGROUND: The role of adenosine in coronary flow regulation becomes increasingly important when KATP channel function or NO synthesis is impaired. Both variables are potentially altered in patients with coronary artery disease taking a sulfonylurea. METHODS: Dose-response curves relating coronary conductance to plasma adenosine concentration were obtained by using intracoronary infusions of adenosine (10 to 1,000 microg/min) in chronically instrumented dogs. RESULTS: ED50, the plasma concentration of adenosine needed to produce 50% of the maximal increase in conductance under baseline conditions, increased threefold after either 1 or 10 mg/kg of L-NAME. ED50 also increased in response to glibenclamide in a dose-related fashion (5.7-fold increase per 1 mg/kg body weight of glibenclamide). Effects of combined blockade of KATP channels and NO synthesis were additive, with increases in ED50 as high as 15-fold. Both L-NAME and glibenclamide increased systemic pressure and reduced coronary conductance, confirming the roles of NO and KATP channels in regulating coronary and systemic vascular tone under rest conditions as well as during stress. CONCLUSIONS: Coronary vascular responsiveness to adenosine is blunted in vivo by both L-NAME and glibenclamide. Effects of the sulfonylurea and blockade of NO synthesis are additive and can limit coronary vasodilation as well as other responses involving KATP channels and NO.

PULMONOLOGY

Author(s): Wen F ; Watanabe K ; Yoshida M

Address: Second Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, 814-0180, Japan.

Title: **Nitric oxide enhances PGI(2)production by human pulmonary artery smooth muscle cells.**

Source: Prostaglandins Leukot Essent Fatty Acids (PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS) 2000 Jun; 62 (6): 369-78

Abstract: To evaluate the effect of exogenous nitric oxide (NO) and endogenous NO on the production of prostacyclin (PGI(2)) by cultured human pulmonary

artery smooth muscle cells (HPASMC) treated with lipopolysaccharide (LPS), interleukin-1(beta)(IL-1(beta)), tumor necrosis factor alpha (TNF(alpha)) or interferon gamma (IFN(gamma)), HPASMC were treated with LPS and cytokines together with or without sodium nitroprusside (SNP), NO donor, N(G)-monomethyl-L-arginine (L-NMMA), NO synthetase inhibitor, and methylene blue (MeB), an inhibitor of the soluble guanylate cyclase. After incubation for 24 h, the postculture media were collected for the assay of nitrite by chemiluminescence method and the assay of PGI(2)by radioimmunoassay. The incubation of HPASMC with various concentrations of LPS, IL-1(beta)or TNF(alpha)for 24 h caused a significant increase in nitrite release and PGI(2)production. However, IFN(gamma)slightly increased the release of nitrite and had little effect on PGI(2)production. Although the incubation of these cells for 24 h with SNP did not cause a significant increase in PGI(2)production, the incubation of HPASMC with SNP and 10 &mgr;g/ml LPS, or with SNP and 100 U/ml IL-1(beta)further increase PGI(2)production and this enhancement was closely related to the concentration of SNP. However, stimulatory effect of SNP on PGI(2)production was not found in TNF(alpha)- and IFN(gamma)- treated HPASMC. Addition of L-NMMA to a medium containing LPS or IL-1(beta)reduced nitrite release and attenuated the stimulatory effect of those agents on PGI(2)production. MeB significantly suppressed the production of PGI(2)by HPASMC treated with or without LPS or IL-1(beta). The addition of SNP partly reversed the inhibitory effect of MeB on PGI(2)production by HPASMC. These experimental results suggest that NO might stimulate PGI(2)production by HPASMC. Exogenous NO together with endogenous NO induced by LPS or cytokines from smooth muscle cells might synergetically enhance PGI(2)production by these cells, possibly in clinical disorders such as sepsis and acute respiratory distress syndrome. Copyright 2000 Harcourt Publishers Ltd.

Author(s): Banning AP ; Prendergast B
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Title: **Intravenous L-arginine reduces VE/VCO2 slope acutely in patients with severe chronic heart failure.**
Source: Eur J Heart Fail (Eur J Heart Fail) 1999 Jun; 1 (2): 187-90
Descriptor: Arginine -- Administration & Dosage
Carbon Dioxide -- Analysis

Heart Failure, Congestive -- Drug Therapy
Pulmonary Gas Exchange -- Drug Effects
Blood Pressure -- Drug Effects
Breath Tests
Chronic Disease
Cross-Over Studies
Exercise Test
Heart Rate -- Drug Effects
Injections, Intravenous
Middle Age
Nifedipine -- Administration & Dosage
Prognosis
Severity of Illness Index
Single-Blind Method
Vasodilator Agents -- Administration & Dosage
Comparative Study
Human
Male

Author(s): Grasemann H ; GSrtig SS ; Wiesemann HG ; Teschler H ; Konietzko N ; Ratjen F
Address: Children's Hospital, University of Essen, Germany.
Title: **Effect of L-arginine infusion on airway NO in cystic fibrosis and primary ciliary dyskinesia syndrome.**
Source: Eur Respir J (EUROPEAN RESPIRATORY JOURNAL) 1999 Jan; 13 (1): 114-8
Abstract: Airway nitric oxide concentrations in patients with cystic fibrosis or primary ciliary dyskinesia syndrome have been shown to be lower than in healthy subjects. Decreased NO concentrations may contribute to impaired ciliary clearance, respiratory tract infections, or obstructive lung disease in these conditions. Nasal and exhaled NO concentrations were compared before and after infusion of 500 mg x kg(-1) L-arginine, the substrate of NO synthases, in 11 cystic fibrosis (CF) patients, seven primary ciliary dyskinesia (PCD) syndrome patients, and 11 control subjects. Baseline nasal and exhaled NO concentrations were significantly lower in both CF and PCD syndrome patients than in controls ($p<0.01$). In controls, the maximum increase of NO was seen immediately after L-arginine infusion in the upper airways (1.8-fold) and 3 h after the infusion in the lower airways (1.4-fold). Although NO concentrations also increased significantly in both CF (1.9-fold and 1.6-fold, respectively) and PCD syndrome patients (1.4-fold and 1.8-fold, respectively), concentrations remained subnormal compared with baseline values of controls. Pulmonary function remained unchanged in both patient groups. In conclusion, the low airway nitric oxide formation

in both cystic fibrosis and primary ciliary dyskinesia syndrome patients can be augmented by L-arginine administration. The finding that pulmonary function remained unchanged in both conditions may be due to the fact that normalization of airway nitric oxide concentrations could not be achieved.

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Title: **Role of nitric oxide in human pulmonary microvascular endothelial cell adhesion**.
Source: Life Sci (LIFE SCIENCES) 2000 May 26; 67 (1): 1-11
Abstract: We examined the effect of nitric oxide (NO) on cell adhesion using cultured human pulmonary microvascular endothelial cells (PMVEC). Attachment of these cells to fibronectin was significantly inhibited by NO donors, spermine NONOate and S-nitroso-N-acetyl-penicillamine or L-arginine, but not 8-bromoguanosine-3',5'-cyclic-monophosphate. Similar results were obtained with the electrical cell-substrate impedance sensor (ECIS) technique. Addition of NO donors or L-arginine, but not 8-bromoguanosine-3',5'-cyclic-monophosphate or N2,2'-O-dibutyrylguanosine-3',5'-cyclic-monophosphate, to confluent PMVEC monolayers resulted in a transient decrease in cell adhesion, which was quantitated by the ECIS. Exposure to 1 U/ml alpha-thrombin reduced the monolayer electrical resistance by approximately 50%. The observed response was significantly suppressed by pretreatment of cells with intracellular calcium chelator, 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid or NO synthase inhibitor, N(G)-nitro-L-arginine methyl ester, but not guanylate cyclase inhibitor, 6-anilino-5,8-quinoline-quinone. Selective knockout of endothelial NO synthase with antisense oligodeoxynucleotides also significantly reduced thrombin-induced decrease in monolayer resistance. Our findings indicate that thrombin stimulates calcium-dependent release of NO from PMVEC, which mediates the retraction of endothelial cells via a cGMP-independent pathway. Our results suggest that NO modulates cell-matrix and/or cell-cell adhesion in PMVEC and that this molecule might modify microvascular permeability in the human lung.

Author(s): Bocchi EA ; Vilella de Moraes AV ; Esteves-Filho A ; Bacal F ; Auler JO ; Carmona MJ ; Bellotti G ; Ramires AF
Address: Heart Institute, Medical School of S‹o Paulo University, Brazil.
Title: **L-arginine reduces heart rate and improves hemodynamics in severe congestive**

heart failure

Source: Clin Cardiol (CLINICAL CARDIOLOGY) 2000 Mar; 23 (3): 205-10

Abstract: BACKGROUND: Stimulated endothelium-derived relaxing factor-mediated vasodilation and conduit artery distensibility are impaired in congestive heart failure (CHF). L-arginine could have a potentially beneficial role in CHF, acting through the nitric oxide (NO)-L-arginine pathway or by growth hormone increment. HYPOTHESIS: This study was undertaken to investigate the effects of L-arginine on heart rate, hemodynamics, and left ventricular (LV) function in CHF. METHODS: In seven patients (aged 39 +/- 8 years) with CHF, we obtained the following parameters using echocardiography and an LV Millar Mikro-Tip catheter simultaneously under four conditions: basal, during NO inhalation (40 ppm), in basal condition before L-arginine infusion, and after L-arginine intravenous infusion (mean dose 30.4 +/- 1.9 g). RESULTS: Nitric oxide inhalation increased pulmonary capillary wedge pressure from 25 +/- 9 to 31 +/- 7 mmHg ($p < 0.05$), but did not change echocardiographic variables or LV contractility by elastance determination. L-arginine decreased heart rate (from 88 +/- 15 to 80 +/- 16 beats/min, $p<0.005$), mean systemic arterial pressure (from 84 +/- 17 to 70 +/- 18 mmHg, $p < 0.007$), and systemic vascular resistance (from 24 +/- 8 to 15 +/- 6 Wood units, $p<0.003$). L-arginine increased right atrial pressure (from 7 +/- 2 to 10 +/- 3 mmHg, $p<0.04$), cardiac output (from 3.4 +/- 0.7 to 4.1 +/- 0.8 l/min, $p < 0.009$), and stroke volume (from 40 +/- 9 to 54 +/- 14 ml, $p < 0.008$). The ratios of pulmonary vascular resistance to systemic vascular resistance at baseline and during NO inhalation were 0.09 and 0.075, respectively, and with L-arginine this increased from 0.09 to 0.12. CONCLUSION: L-arginine exerted no effect on contractility; however, by acting on systemic vascular resistance it improved cardiac performance. L-arginine showed a negative chronotropic effect. The possible beneficial effect of L-arginine on reversing endothelial dysfunction in CHF without changing LV contractility should be the subject of further investigations.

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Title: **Nitric oxide spares myocardial oxygen consumption through attenuation of contractile response to beta-adrenergic stimulation in patients with idiopathic dilated cardiomyopathy.**

Source: Circulation (CIRCULATION) 2000 Apr 25; 101 (16): 1925-30

Abstract: BACKGROUND: The results of recent studies suggest that NO synthase may increase in the failing myocardium and that NO modulates the myocardial contractile response to beta-adrenergic stimulation. However, there are few data regarding the physiological role of NO in patients with heart failure. The aim of the present study was to address the role of NO in left ventricular (LV) contractile response to beta-adrenergic stimulation and corresponding oxygen expenditure in human heart failure. METHODS AND RESULTS: We studied 15 patients with heart failure due to idiopathic dilated cardiomyopathy (mean ejection fraction 0.33). We examined LV contractility (E(max), the slope of end-systolic pressure-volume relation), LV external work (EW), myocardial oxygen consumption (MVO(2)), and mechanical efficiency (measured as EW/MVO(2)) with the use of conductance and coronary sinus thermodilution catheters before and during dobutamine (DOB) infusion via a peripheral vein (4. 8+/-0.3 microg. kg(-1). min(-1) IV). Heart rate was kept constant with atrial pacing. We carried out a similar protocol during the intracoronary infusion of the NO synthase inhibitor N(G)-monomethyl-L-arginine (L-NMMA; 200 micromol). DOB increased E(max), EW, and MVO(2) (by 77+/-17%, 39+/-5%, and 21+/-5%, respectively), leading to an increase in mechanical efficiency (25.4+/-3.1% to 29.6+/-4.1%). L-NMMA alone did not significantly change these variables. Although the concurrent infusion of DOB with L-NMMA increased E(max), EW, and MVO(2) (by 140+/-21%, 64+/-9%, and 35+/-5%, respectively) more than DOB alone, mechanical efficiency did not increase further (24.3+/-3.3% to 29.5+/-4.5%) because EW and MVO(2) increased in parallel. Conclusions-These data suggest that in patients with idiopathic dilated cardiomyopathy, endogenous NO spares MVO(2) through attenuation of LV contractile response to beta-adrenergic stimulation while maintaining LV energy-converting efficiency.

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Title: **Nitric oxide: biological role and clinical uses.**

Source: Indian J Pediatr (INDIAN JOURNAL OF PEDIATRICS) 1998 May-Jun; 65 (3): 333-45

Abstract: Nitric oxide is a product of the conversion of

L-arginine by the enzyme nitric oxide synthase. Nitric oxide is involved in a variety of physiological situations and is produced by many different cell types. It is involved in neurotransmission, maintenance of vascular smooth muscle tone, and cytotoxicity. Nitric oxide has been suggested to play an anti-inflammatory role by inhibiting the expression of the genes for inflammatory cytokines. The pathophysiological role of nitric oxide is also evident in a variety of diseases, including septic shock, asthma, reperfusion injury, etc. Nitric oxide, by stimulating the production of cyclic GMP, relaxes smooth muscles of the cardiovascular, respiratory, gastrointestinal, and genito-urinary systems. Recent studies have provided important information on the use of inhaled nitric oxide for the management of several diseases characterized by the presence of abnormal pulmonary vascular tone, such as persistent pulmonary hypertension of the newborn. This review addresses the biology and clinical uses of inhaled nitric oxide.

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Title: **Nitric oxide attenuates normal and sickle red blood cell adherence to pulmonary endothelium.**
Source: Am J Hematol (AMERICAN JOURNAL OF HEMATOLOGY) 2000 Apr; 63 (4): 200-4
Abstract: Increased adherence of sickle red blood cells (RBC) to endothelium is implicated as an initiating event of vaso-occlusion in sickle cell disease. Although much is known about the humoral influences of this interaction, there has been little investigation regarding endothelial contributions. Endothelial derived nitric oxide (NO) inhibits adhesion of platelets and leukocytes to endothelium and decreases expression of VCAM-1, an endothelial adhesion site implicated in sickle RBC/endothelial adherence. However, whether NO inhibits RBC adherence to endothelium is unexplored. We tested this hypothesis with endothelial monolayers exposed to RBC from normal (Hb AA) and sickle cell (Hb SS) volunteers in a parallel plate flow chamber. To decrease NO production, endothelial monolayers were exposed to 100 &mgr;M nitro-L-arginine (NLA), an inhibitor of nitric oxide synthase, resulting in an 87% increase in normal RBC adherence (P = 0.002). Because adherence of normal RBC to endothelium was low, the effect of DETA-NO, an NO donor, was tested after activation of endothelium with TNF-alpha

increased adherence by 130% (P < 0.001). Subsequent addition of 2 mM DETA-NO produced a 75% decrease in adherence of normal RBC to endothelium (P = 0.03). At baseline, sickle RBC were significantly more adherent than normal RBC (P < 0.001) and DETA-NO decreased sickle RBC adherence by 54% (P = 0.04). Thus, NO inhibits both normal and sickle RBC adherence to endothelium. Strategies that enhance NO activity may be therapeutic in sickle cell disease. Copyright 2000 Wiley-Liss, Inc.

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Title: **Nitric oxide modulates interleukin-1beta and tumor necrosis factor-alpha synthesis by alveolar macrophages in pulmonary tuberculosis**.

Source: Am J Respir Crit Care Med (AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE) 2000 Jan; 161 (1): 192-9

Abstract: Interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha released from alveolar macrophages (AM) in pulmonary tuberculosis (TB) are important in host defense against mycobacterial infection. Nitric oxide (NO) production is enhanced in AM of TB patients. We examined whether NO was implicated in (IL)-1beta and TNF-alpha synthesis by AM of TB patients. Purified AM were retrieved by bronchoalveolar lavage from 11 TB patients and 10 normal subjects, and were cultured with or without the NO inhibitor N(G)-monomethyl-L-arginine (L-NMMA). The release of IL-1beta and TNF-alpha, and expression of their messenger RNAs (mRNAs), were determined by enzyme-linked immunosorbent assay and Northern blot analysis. The release of IL-1beta and TNF-alpha was greater from AM of TB patients than from AM of normal subjects. L-NMMA inhibited nitrite, IL-1beta, and TNF-alpha production in TB patients. The mRNA expression for IL-1beta and TNF-alpha was upregulated in TB patients and was depressed by L-NMMA. Immunocytochemistry done with a monoclonal antibody against the p65 subunit of nuclear factor (NF)-kappaB showed that NF-kappaB was highly expressed and translocated to the nuclei of AM from TB patients, and was inhibited by L-NMMA. Inhibition of NF-kappaB by pyrrolidine dithiocarbamate attenuated IL-1beta and TNF-alpha synthesis. In conclusion, enhanced NO generation by AM of TB patients plays an autoregulatory role in amplifying the synthesis of proinflammatory cytokines, probably through NF-kappaB activation.

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Title: **Arginine nutrition in development, health and disease.**
Source: Curr Opin Clin Nutr Metab Care (Curr Opin Clin Nutr Metab Care) 2000 Jan; 3 (1): 59-66
Abstract: As a precursor of nitric oxide, polyamines and other molecules with enormous biologic importance, L-arginine plays versatile key roles in nutrition and metabolism. Arginine is an essential amino acid in the fetus and neonate, and is conditionally an essential nutrient for adults, particularly in certain disease conditions. L-Arginine administration is beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, and in facilitating wound healing. The effect of L-arginine in treating many common health problems is unique among amino acids, and offers great promise for improved health and well-being in the future.

Author(s): Ashutosh K
Address: Veterans Administration Medical Center at Syracuse and SUNY Health Science Center, NY 13210, USA.
Title: **Nitric oxide and asthma: a review.**
Source: Curr Opin Pulm Med (CURRENT OPINION IN PULMONARY MEDICINE) 2000 Jan; 6 (1): 21-5
Abstract: Nitric oxide (NO) is synthesized from the amino acid arginine by enzymes called nitric oxide synthases. NO has an important physiologic role in the regulation of vascular tone, response to vascular injury, and hemostasis. It also acts as a neurotransmitter for the nonadrenergic noncholinergic nerves and has important antimicrobial, immunologic, and proinflammatory activities. The lung is rich in nitric oxide synthases, and NO is normally present in the exhaled air. Use of NO in the treatment of asthma has not withstood the test of time and is not recommended. With the advent of analyzers capable of measuring NO rapidly and reliably, however, the analysis of NO in exhaled air is being increasingly recognized as a potential noninvasive test for the evaluation of the inflammatory component of the pathology of patients with asthma. An increase in the exhaled NO has been shown to accompany eosinophilic inflammation and to correlate with other indices of inflammation in asthma. Exhaled NO increases during exacerbation and decreases with

recovery in patients with asthma. As exhaled NO is not increased during bronchospasm in the absence of coexisting inflammation, it could serve to differentiate between the inflammatory and bronchospastic components in asthma, thereby guiding therapy with steroids and other anti-inflammatory medications. Levels of NO also can be increased in certain other conditions, for example, allergic rhinitis and adult respiratory distress syndrome, but these can be clinically differentiated from asthma and do not lessen the diagnostic value of exhaled NO. Measurements of exhaled NO are influenced by several physiologic and technical variables, which results in a wide variation in the levels reported from the different laboratories. Standardization of technique, a better understanding of the confounding effects of physiologic and environmental variables, and establishment of the normal range and variability of exhaled NO are needed before its measurement could gain wide acceptance as a clinically useful test. Development of less expensive NO analyzers is also an important consideration.

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Address: Department of Animal Sciences, Rutgers University, New Jersey, 08903, New Brunswick.
Title: **L-arginine reduces right heart hypertrophy in hypoxia-induced pulmonary hypertension.**
Source: Biochem Biophys Res Commun (BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS) 1999 Jan 8; 254 (1): 100-3
Abstract: Endothelin (Et) and nitric oxide (NO) may serve as chemical mediators of hypoxia-induced pulmonary hypertension. Plasma levels of Et1 were elevated 2-fold while levels of nitrate, a NO metabolite, decreased in rats exposed to 10 days of hypoxia (10% O2). Administration of l-arginine, the precursor for NO, decreased Et, increased nitrate, and decreased right ventricular hypertrophy in hypoxic animals. By increasing plasma NO levels, the right ventricular hypertrophy and right heart failure seen in hypoxia-induced pulmonary hypertension in human patients may be prevented.

Author(s): Cremona G ; Higenbottam TW ; Bower EA ; Wood AM ; Stewart S
Address: Pulmonary Division, "Salvatore Maugeri" Foundation IRCCS, Medical Centre, Veruno, Italy.
Title: **Hemodynamic effects of basal and stimulated release of endogenous nitric oxide in isolated human lungs.**
Source: Circulation (CIRCULATION) 1999 Sep 21; 100 (12): 1316-21

Abstract: Background-We compared the hemodynamic responses to inhibition or stimulation of endothelial nitric oxide (NO) release of isolated explanted lungs from transplantation recipients with pulmonary hypertension and in normotensive unallocated donor lungs. Methods and Results-Lungs from 10 patients with severe pulmonary hypertension (SPH) and from 16 patients with severe chronic obstructive lung disease (COLD) were studied. Fourteen normotensive lungs were studied as controls. The lungs were perfused at a constant flow. In protocol 1 N(G)-nitro-L-arginine methyl ester caused a similar rise in baseline pulmonary artery pressure (PAP) that was similar in SPH (+17.1+/-4.2 mm Hg; n=5), COLD (+15.5+/-4.8 mm Hg; n=8), and control lungs (+14.5+/-1.5 mm Hg; n=7). Arterial occlusion demonstrated that most of the changes with N(G)-nitro-L-arginine methyl ester were precapillary. The response to sodium nitroprusside (10(-8) to 10(-4) mol/L) was similar in all groups. In protocol 2, the lungs were preconstricted, and acetylcholine (10(-9) to 10(-5) mol/L) caused a lesser fall in PAP in both COLD and SPH lungs compared with control (-41.9+/-8.6%, -55. 7+/-7.6%, and -73.2+/-2.5%, respectively; P<0.05), whereas sodium nitroprusside (10(-5) mol/L) decreased PAP to initial levels in all lungs. Conclusions-Stimulated release of NO is impaired in arteries of lungs with plexogenic or hypoxemic pulmonary hypertension. In contrast, basal release of NO appears to be maintained.

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Address: Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA.
Title: **Nitric oxide and pulmonary hypertension.**
Source: Coron Artery Dis (CORONARY ARTERY DISEASE) 1999 Jul; 10 (5): 287-94
Abstract: The constitutive release of NO by the endothelium plays a key role in maintaining normal low basal pulmonary vascular tone and countering hypoxic vasoconstrictive tone in many mammals and in humans. Many, but not all, studies have suggested that reduced availability of NO contributes to the increased pulmonary vascular resistance that occurs in experimental models and in humans with pulmonary hypertension. Potential mechanisms limiting the activity of NO include L-arginine deficiency and a reduction in eNOS expression or message stability. Inhaled NO therapy may overcome some of these abnormalities, improving oxygenation and reducing pulmonary artery pressure in patients with primary and secondary forms of pulmonary hypertension.

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Address: Department of Paediatrics, Royal Brompton and Harefield NHS Trust, National Heart and Lung Institute (Imperial College of Science, Technology and Medicine), London, UK.
Title: **L-arginine and substance P reverse the pulmonary endothelial dysfunction caused by congenital heart surgery**.
Source: Circulation (CIRCULATION) 1999 Aug 17; 100 (7): 749-55
Abstract: BACKGROUND: The increase in pulmonary vascular resistance (PVR) seen in children after cardiopulmonary bypass has been attributed to transient pulmonary endothelial dysfunction (PED). We therefore examined PED in children with congenital heart disease by assessing the L-arginine-nitric oxide (NO) pathway in terms of substrate supplementation (L-arginine [L-Arg]), stimulation of endogenous NO release (substance P [Sub-P]), and end-product provision (inhaled NO) before and after open heart surgery. METHODS AND RESULTS: Ten patients (aged 0.62+/-0.27 years) with pulmonary hypertension undergoing cardiac catheterization who had not had surgery and 10 patients (aged 0.65+/-0.73 years) who had recently undergone cardiopulmonary bypass were examined. All were sedated and paralyzed and received positive-pressure ventilation. Blood samples and pressure measurements were taken from catheters in the pulmonary artery and the pulmonary vein or left atrium. Respiratory mass spectrometry was used to measure oxygen uptake, and cardiac output was determined by the direct Fick method. PVR was calculated during steady state at ventilation with room air, during FIO(2) of 0.65, then during additional intravenous infusion of L-Arg (15 mg. kg(-1). min(-1)) and Sub-P (1 pmol. kg(-1). min(-1)), and finally during inhalation of NO (20 ppm). In preoperative patients, the lack of an additional significant change of PVR with L-Arg, Sub-P, and inhaled NO suggests little preexisting PED. Postoperative PVR was higher, with an additional pulmonary endothelial contribution that was restorable with L-Arg and Sub-P. CONCLUSIONS: Postoperatively, the rise in PVR suggested PED, which was restorable by L-Arg and Sub-P, with no additional effect of inhaled NO. These results may indicate important new treatment strategies for these patients.

Author(s): Fagan JM ; Rex SE ; Hayes-Licitra SA ; Waxman L
Address: Department of Animal Sciences, Rutgers University, New Jersey, 08903, New Brunswick.
Title: **L-arginine reduces right heart hypertrophy in hypoxia-induced pulmonary hypertension.**
Source: Biochem Biophys Res Commun (BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS) 1999 Jan 8; 254 (1): 100-3
Abstract: Endothelin (Et) and nitric oxide (NO) may serve as chemical mediators of hypoxia-induced pulmonary hypertension. Plasma levels of Et1 were elevated 2-fold while levels of nitrate, a NO metabolite, decreased in rats exposed to 10 days of hypoxia (10% O2). Administration of l-arginine, the precursor for NO, decreased Et, increased nitrate, and decreased right ventricular hypertrophy in hypoxic animals. By increasing plasma NO levels, the right ventricular hypertrophy and right heart failure seen in hypoxia-induced pulmonary hypertension in human patients may be prevented. Copyright 1999 Academic Press.

Author(s): Ceneviva GD ; Tzeng E ; Hoyt DG ; Yee E ; Gallagher A ; Engelhardt JF ; Kim YM ; Billiar TR ; Watkins SA ; Pitt BR
Address: Division of Pediatric Critical Care Medicine, Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA.
Title: **Nitric oxide inhibits lipopolysaccharide-induced apoptosis in pulmonary artery endothelial cells.**
Source: Am J Physiol (AMERICAN JOURNAL OF PHYSIOLOGY) 1998 Oct; 275 (4 Pt 1): L717-28
Abstract: Our group recently reported that cultured sheep pulmonary artery endothelial cells (SPAECs) became resistant to lipopolysaccharide (LPS)-induced apoptosis several days after constitutive synthesis of nitric oxide (NO) after adenoviral (Ad) transfer of inducible NO synthase (iNOS) or exposure to the NO donor S-nitroso-N-acetylpenicillamine (SNAP) (E. Tzeng, Y.-M. Kim, B. R. Pitt, A. Lizonova, I. Kovesdi, and T. R. Billiar. Surgery 122: 255-263, 1997). In the present study, we confirmed this observation by establishing stable transfectants after retroviral gene transfer [replication-deficient retrovirus (DFG)] of human iNOS (DFG-iNOS) SPAECs and then used all three approaches (Ad, DFG, and SNAP) to determine underlying mechanisms of this phenomenon. Continuous endogenous production of NO in itself did not cause apoptosis as assessed by phase-contrast microscopy, nuclear morphology, and internucleosomal DNA fragmentation. Prolonged (72-96 h) synthesis of NO, however, after DFG- or

replication-deficient adenovirus (Ad. CMV)-iNOS or SNAP (100 microM, 96 h) inhibited LPS-induced apoptosis. The kinetics of such protection suggested that NO may be inducing other gene products. Ad-mediated transfer of manganese superoxide dismutase (MnSOD) decreased the sensitivity of wild-type SPAECs to LPS-induced apoptosis. MnSOD, however, was not induced in an NG-monomethyl-L-arginine (L-NMMA)-sensitive time-dependent fashion after Ad.CMV-iNOS. Other inducible genes that may be affected by NO and that may protect against potential oxidant-mediated LPS-induced apoptosis including 70-kDa heat shock protein, heme oxygenase-1, metallothionein, and Bcl-2 also were not elevated in an L-NMMA-sensitive, time-dependent fashion. Although the candidate gene product underlying NO-induced protection remains unclear, we did note that prolonged synthesis of NO inhibited LPS-induced activation of an interleukin-1beta-converting enzyme-like cysteine protease (cysteine protease protein-32-like) in a dithiothreitol-sensitive fashion, suggesting that S-nitrosylation of an important downstream target of convergence of apoptotic signals may contribute to the sensitivity of SPAECs to LPS.

Author(s): Cooper CJ ; Jevnikar FW ; Walsh T ; Dickinson J ; Mouhaffel A ; Selwyn AP
Address: Department of Medicine, Medical College of Ohio, Toledo 43699-0008, USA.
Title: **The influence of basal nitric oxide activity on pulmonary vascular resistance in patients with congestive heart failure**.
Source: Am J Cardiol (AMERICAN JOURNAL OF CARDIOLOGY) 1998 Sep 1; 82 (5): 609-14 Journal Code: 3DQ
Additional Info: UNITED STATES
Standard No: ISSN: 0002-9149
Language: ENGLISH
Abstract: Increased pulmonary resistance may reduce survival and treatment options in patients with congestive heart failure. Nitric oxide (NO) is a determinant of normal pulmonary resistance vessel tone. We tested the hypothesis that loss of NO function contributes to increased pulmonary vascular resistance index (PVRI) in congestive heart failure. Pulmonary arterial resistance vessel function was studied in 25 conscious adults. Three groups were studied: 8 controls, 9 patients with congestive heart failure and normal PVRI, and 8 patients with congestive heart failure and raised PVRI. Segmental arterial flow was determined with a Doppler wire and quantitative angiography.

NG-monomethyl-L-arginine (L-NMMA) was used to inhibit NO, whereas phenylephrine was used as an endothelium-independent control. The response to inhibition of NO with L-NMMA was less in patients with congestive heart failure and elevated PVRI than in patients with congestive heart failure and normal PVRI ($p < 0.05$). The difference in response between the congestive heart failure groups was specific to NO-dependent regulation because the response to the endothelium-independent constrictor phenylephrine was not different ($p = 0.92$). There was no difference in response to L-NMMA between controls and patients with congestive heart failure and normal PVRI. The response to L-NMMA correlated to PVRI. In adults with congestive heart failure, NO appears to play an important role in maintaining normal pulmonary resistance.

Author(s): al-Ali MK ; Howarth PH
Address: University Medicine, Southampton General Hospital, U.K.
Title: **Nitric oxide and the respiratory system in health and disease.**
Source: Respir Med (RESPIRATORY MEDICINE) 1998 May; 92 (5): 701-15
MESH Subject(s) below:
Descriptor: Lung Diseases -- Metabolism
Nitric Oxide -- Physiology
Respiratory System -- Metabolism
Arginine -- Metabolism
Biological Markers -- Analysis
Graft Rejection -- Metabolism
Lung Transplantation
Models, Biological
Nitric-Oxide Synthase -- Metabolism
Pulmonary Gas Exchange
Animal
Human
Support, Non-U.S. Gov't

Author(s): Tun*tan B ; Okur H ; Calisir CH ; Abacioglu H ; Cakici I ; Kanzik I ; Abacioglu N
Address: Department of Pharmacology, Faculty of Pharmacy, Gazi University, Ankara, Turkey.
Title: **Comparison of nitric oxide production by monocyte/macrophages in healthy subjects and patients with active pulmonary tuberculosis.**
Source: Pharmacol Res (PHARMACOLOGICAL RESEARCH) 1998 Mar; 37 (3): 219-26
Abstract: The aim of the present study was to determine the NO production by human cultured macrophages (m phi) and to compare the NO production between healthy subjects and patients with active pulmonary tuberculosis. The bioassay method was used for

assessment of validation. Lipopolysaccharide (125 ng ml-1)-activated m phi from healthy and diseased subjects released a substantial amount of NO. NO synthase inhibitor, NG-nitro-L-arginine methyl ester, (0.1 mmol l-1) suppressed NO synthesis significantly in m phi of healthy subjects. Nitrite formation measured by the diazotization method in the supernatants taken from cultured m phi of tuberculous patients were significantly lower than the healthy subjects. The supernatants obtained in both subjects caused relaxation of guinea-pig aorta reversed by methylene blue (10 mumol l-1). There was a significant difference between relaxations of healthy and diseased supernatants. Nitrite formation measured by the bioassay method in the supernatants taken from cultured m phi of tuberculous patients was significantly higher than the healthy subjects. It was concluded that NO production appeared to be decreased in tuberculosis. The reason for decreased production of NO in tuberculosis may be related to the interaction of several cytokines and/or eicosanoids by means of the disease related induction of immune reactions.

Author(s): Babaei S ; Teichert-Kuliszewska K ; Monge JC ; Mohamed F ; Bendeck MP ; Stewart DJ
Address: Terrence Donnelly Heart Centre, St. Michael's Hospital, Department of Medicine, University of Toronto, Ontario, Canada.
Title: Role of nitric oxide in the angiogenic response in vitro to basic fibroblast growth factor.
Source: Circ Res (CIRCULATION RESEARCH) 1998 May 18; 82 (9): 1007-15
Abstract: Angiogenesis is a complex process that involves the activation of quiescent endothelial cells (ECs) to a proliferative and migratory phenotype and, subsequently, their redifferentiation to form vascular tubes. We hypothesized that NO contributes to angiogenesis by terminating the proliferative action of angiogenic growth factors and initiating a genetic program of EC differentiation. Human umbilical vein ECs (HUVECs) and calf pulmonary artery ECs (CPAECs) were grown directly on plastic dishes or on three-dimensional fibrin matrices. In the absence of fibrin, treatment with NO-donor compounds, such as S-nitroso-N-acetylpenicillamine (SNAP, 0.1 and 0.4 mmol/L), produced a dose-dependent inhibition of proliferation in both cell lines, whereas the inhibition of endogenous NO production using NG-nitro-L-arginine methyl ester (L-NAME, 1 mmol/L) or NG-monomethyl-L-arginine (L-NMMA, 1 mmol/L) significantly increased

proliferation of the CPAECs. The addition of basic fibroblast growth factor (bFGF, 30 ng/mL) increased the expression of endothelial NO synthase mRNA and the production of NO in both cell types when cultured on three-dimensional fibrin gels and produced profound morphological changes characterized by the appearance of extensive capillary-like vascular structures and the loss of EC monolayers. These changes were quantified by measuring total tube length per low-power field (x100), and a differentiation index was derived using the ratio of tube length over area covered by residual EC monolayer. In the absence of additional angiogenic factors, the differentiation index was low for both HUVECs and CPAECs (control, 1.16+/-0.19 and 2.07+/-0.87, respectively). Treatment with bFGF increased the differentiation index significantly in both cell types (10.59+/-2.03 and 20.02+/-5.01 for HUVECs and CPAECs, respectively; P<.05 versus control), and the addition of SNAP (0.4 mmol/L) mimicked the angiogenic response to bFGF (8.57+/-1.34 and 12.20+/-3.49 for HUVECs and CPAECs, respectively; P<.05 versus control). Moreover, L-NAME inhibited EC tube formation in response to bFGF in a dose-response manner, consistent with a role of endogenous NO production in EC differentiation in this angiogenic model. These findings suggest that NO may act as a crucial signal in the angiogenic response to bFGF, terminating the proliferative actions of angiogenic growth factors and promoting EC differentiation into vascular tubes.

Author(s): Hojo S ; Fujita J ; Miyawaki H ; Obayashi Y ; Takahara J ; Bartholomew DW
Address: First Department of Internal Medicine, Kagawa Medical University, Japan.
Title: Severe cystic fibrosis associated with a deltaF508/R347H + D979A compound heterozygous genotype.
Source: Clin Genet (CLINICAL GENETICS) 1998 Jan; 53 (1): 50-3 Journal Code: DDT
Additional Info: DENMARK
Standard No: ISSN: 0009-9163
Language: ENGLISH
Abstract: This report is concerned with twins with cystic fibrosis (CF). They are of mixed parentage: Japanese mother and German father. One case is presented with meconium ileus as a neonate. The other patient did relatively well until the age of 6 years when she was first hospitalized and diagnosed with pulmonary aspergillosis. They have been receiving standard therapies for CF including

digestive enzymes, vitamins and periodic antibiotic therapy in the US. At 19 years of age, they were tested for common mutations and one AF508 cystic fibrosis transmembrane conductance regulator (CFTR) allele was found. Further testing of their CFTR gene as well as those of their Japanese mother and grandmother revealed missense mutations in exon 7 (R347H) and exon 16 (D979A). Although the D979A mutant is very rare, this mutation combination seemed to be responsible for severe CF phenotypes.

MESH Subject(s) below:

Descriptor: Alanine -- Genetics
Arginine -- Genetics
Asparagine -- Genetics
Cystic Fibrosis -- Genetics
Cystic Fibrosis Transmembrane Conductance Regulator -- Genetics
Heterozygote
Histidine -- Genetics
Adult
Genotype
Point Mutation
Severity of Illness Index
Case Report
Female
Human
Male

Chemical Subst: 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)
6898-94-8 (Alanine)
7004-12-8 (Arginine)
7006-34-0 (Asparagine)
7006-35-1 (Histidine)

RHEUMATOLOGY

Author(s): Khan F ; Belch JJ

Address: University Department of Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, UK.

Title: **Skin blood flow in patients with systemic sclerosis and Raynaud's phenomenon: effects of oral L-arginine supplementation.**

Source: J Rheumatol (JOURNAL OF RHEUMATOLOGY) 1999 Nov; 26 (11): 2389-94 Journal Code:JWX

Abstract: OBJECTIVE: To measure skin blood flow responses to the iontophoresis of acetylcholine and sodium nitroprusside in the digits of patients with systemic sclerosis (SSc) and control subjects.Additionally, to test the effects of oral L-arginine supplementation versus placebo in patients. METHODS: Skin blood flow was measured at the dorsum of the finger using laser Doppler flowmetry during iontophoresis of endothelium dependent (acetylcholine) and independent (sodium nitroprusside) vasodilators. L-arginine and placebo supplementation were given in a double blind, crossover fashion (8 g daily for 28 days). RESULTS: In comparison to

control subjects, dose dependent vascular responses to acetylcholine were diminished in patients with SSc (1.7 +/- 0.3, 3.6 +/- 0.7, 5.9 +/- 1.5 vs 1.4 +/- 0.1, 2.4 +/- 0.6, 2.4 /- 0.5; p < 0.01, ANOVA). Vascular responses to sodium nitroprusside were not significantly different between control subjects and SSc patients. L-arginine supplementation, however, had no significant effect on vascular responses to acetylcholine and sodium nitroprusside. CONCLUSION: There is an abnormality of endothelial dependent vasodilatation in the digital vasculature of patients with SSc. The lack of effect of supplementation with L-arginine suggests the abnormality may be independent of the L-arginine/nitric oxide pathway and may involve prostanoids

Author(s): Henrotin YE ; Zheng SX ; Deby GP ; Labasse AH ; Crielaard JM ; Reginster JY
Address: Bone and Cartilage Metabolism Research Unit, Institute of Pathology, University of Liege, Belgium.
Title: **Nitric oxide downregulates interleukin 1beta (IL-1beta) stimulated IL-6, IL-8, and prostaglandin E2 production by human chondrocytes [see comments]**
Source: J Rheumatol (JOURNAL OF RHEUMATOLOGY) 1998 Aug; 25 (8): 1595-601 Journal Code:JWX
Abstract: OBJECTIVE: To investigate the effects of endogenously produced nitric oxide (NO) on interleukin 6 (IL-6), IL-8, prostaglandin E2 (PGE2), and proteoglycan production by human chondrocytes. METHODS: Human articular chondrocytes were isolated from their extracellular matrix by triple successive enzymatic digestion of the cartilage and cultured 48 h in a well defined culture medium. IL-6 and IL-8 were directly assayed into culture media by specific enzyme amplified sensitivity immunoassays. Proteoglycans and PGE2 were quantified by specific radioimmunoassays. Cell culture media were assayed for NO2 using a spectrophotometric assay based upon the Griess reaction. RESULTS: Unstimulated chondrocytes produced low levels of NO, IL-6, IL-8, and PGE2. Production was significantly stimulated by IL-1beta and lipopolysaccharide (LPS). As well, proteoglycan synthesis was profoundly inhibited by IL-1beta and LPS. Inhibition of NO synthesis with the competitive inhibitor NG-monomethyl-L-arginine (L-NMMA) led to enhancement of IL-6, IL-8, and PGE2 production stimulated by either IL-1beta alone or in combination with LPS, whereas the inhibition of proteoglycan production by IL-1beta was not modified by L-NMMA. CONCLUSION: LPS and IL-1beta stimulated IL-6, IL-8, and PGE2 production are downregulated by endogenously produced NO, which could limit the inflammatory reaction occurring in arthritis.

Author(s): Stichtenoth DO ; Frslich JC
Address: Department of Clinical Pharmacology, Hannover Medical School, Germany.
Title: **Nitric oxide and inflammatory joint diseases.**
Abstract: Nitric oxide (NO) is synthesized from L-arginine by the NO synthases. At present, mainly three NO synthase isoenzyme groups are differentiated: two constitutive NO synthases, responsible for homeostatic cardiovascular and neuronal functions of NO, and an inducible NO synthase. After induction by certain cytokines or endotoxin, this latter isoform produces large quantities of NO with cyto- and bacteriotoxic effects. High amounts of

NO, synthesized systemically and intra-articularly, play an important role in inflammatory joint diseases, as shown in animal models of arthritis and in patients with rheumatoid arthritis or spondyloarthropathies. In experimental arthritis, administration of NO synthase inhibitors profoundly reduced disease activity. In humans, beneficial effects of NO synthesis inhibition are inferred from indirect evidence: glucocorticoids, inhibiting induction of the inducible NO synthase, reduce enhanced NO synthesis and disease activity. Thus, selective inhibition of the pathologically enhanced NO synthesis emerges as a new experimental therapeutic approach in the treatment of inflammatory joint diseases.

Author(s): Grabowski PS ; Macpherson H ; Ralston SH
Address: Department of Medicine &Therapeutics, University of Aberdeen, UK.
Title: **Nitric oxide production in cells derived from the human joint.**
Source: Br J Rheumatol (BRITISH JOURNAL OF RHEUMATOLOGY) 1996 Mar; 35 (3): 207-12
Abstract: We have investigated the ability of cells derived from the human joint to generate nitric oxide (NO). Synovial fibroblasts, articular chondrocytes and osteoblasts were cultured from tissues of patients undergoing hip replacement surgery, and synovial fluid leucocytes were obtained from patients undergoing joint aspiration. There was little spontaneous generation of NO by any of the cells after culture, but synovial fibroblasts, articular chondrocytes and osteoblasts all produced large quantities of NO in response to a cytokine mix of interleukin (IL)-1 beta + tumour necrosis factor alpha (TNF alpha) + interferon (IFN gamma). Reverse transcription-polymerase chain reaction (RT-PCR) analysis showed the presence of mRNA transcripts for the inducible isoform of NO synthase in cytokine-stimulated but not in unstimulated cells. In contrast, leucocytes from synovial fluid did not produce NO either spontaneously or after cytokine stimulation, and mRNA for inducible NO synthase (iNOS) was not detected in these cells even by nested PCR. There were significant differences in the regulation of NO production between chondrocytes and other cells. Only chondrocytes generated NO in response to IL-1 beta or TNF alpha alone, whereas synovial fibroblasts and osteoblasts required the presence of at least two cytokines to generate NO. Dexamethasone (10(-6)M) had a small but significant inhibitory effect on NO production by chondrocytes, synovial fibroblasts and osteoblasts. Our results indicate that several cells within the human joint have the potential to generate NO in the presence of an appropriate pro-inflammatory cytokine stimulus, while leucocytes in synovial fluid are not a significant source of NO. The data support suggestions that NO is produced within the inflamed joint in diseases such as rheumatoid arthritis.

Author(s): Weyand CM ; Goronzy JJ
Address: Department of Medicine, Mayo Clinic and Foundation, Rochester, MN 55905, USA.
Title: **Inherited and noninherited risk factorsin rheumatoid arthritis.**
Source: Curr Opin Rheumatol (CURRENT OPINION IN RHEUMATOLOGY) 1995 May; 7 (3): 206-13
Abstract: Rheumatoid arthritis (RA) is likely the result of a concerted action of several inherited and noninherited factors. Although there is a high suspicion that

environmental factors are important, proof is missing. Most information has been collected on genetic risk factors. The inheritance pattern for RA is complex, and there is good evidence that HLA as well as non-HLA genes are involved. Almost all racial-ethnic groups share the association of RA with the HLA-DRB1-encoded sequence motif QKRAA or QRRAA. However, the completeness of the association varies significantly in different ethnic cohorts, as can be expected in a multigene model. The sequence motif translates into a pocket in the antigen-binding site of the HLA-DR molecule. The "rheumatoid pocket" accommodates peptide side chains and has distinct binding characteristics. Epidemiologic evidence points toward a role for non-HLA genes. Candidate genes, such as transporter in antigen processing (TAP) genes are currently explored. Major advances in defining and understanding the contribution of inherited and noninherited factors in RA may come from abandoning the concept of RA as a single entity and accepting a heterogeneity model for RA. Distributions of HLA-DR genes indicate that several subsets of RA patients exist. Seronegative (prognostically good) and seropositive (prognostically worse) patients can be distinguished by the arginine versus lysine substitution at position 71 of the HLA-DRB1 gene. A different dimension of disease, rheumatoid organ disease, appears to be reached in patients with two HLA-DRB1*0401 alleles. Identification of distinct RA subsets may allow us to stratify patients into categories that differ with respect to etiology, disease course, clinical pattern, and treatment response.

Author(s): Abramson S ; Belmont HM ; Hopkins P ;
Buyon J ; Winchester R ; Weissmann G

Title:
Complement activation and vascularinjury in systemic lupus erythematosus.

Source: J Rheumatol (JOURNAL OF RHEUMATOLOGY)
1987 Jun; 14 Suppl 13: 43-6

Abstract: The deposition of immune complexes within blood vessel walls results in the potential for complement activation and the release of chemotactic factors, such as fragments of C5 (C5fr). The generation of C5fr results in the intravascular aggregation of neutrophils with subsequent leukostatic occlusion of the pulmonary arterioles. The generation of C5fr may contribute to the pathogenesis of adult respiratory distress syndrome and other diseases. Studies were undertaken to determine the role of circulating complement derived peptides and intravascular neutrophil activation in systemic lupus erythematosus.

Author(s): Trang LE ; FŸrst P ; OdebSck AC ;
Lsvgren O

Title: Plasma amino acids in rheumatoid arthritis.

Source: Scand J Rheumatol (SCANDINAVIAN JOURNAL
OF RHEUMATOLOGY) 1985; 14 (4): 393-402

Abstract: Plasma amino acid concentrations have been investigated in 12 female patients with rheumatoid arthritis (RA), who were hospitalized for two 14-day periods, one of which included 7 days of total fasting, whereas the other served as control period with normal food intake. All medical treatment was stopped on admission to the hospital. Plasma amino acid levels were repeatedly determined during both periods. Another group, consisting of 8 healthy volunteers, also underwent total fasting, for 6 days.

The response to food deprivation with regard to plasma amino acid levels was compared with that in the RA patients. The results obtained from the control period were compared with those derived from age and sex matched healthy controls. RA disease was not characterized by a typical amino acid pattern. Major increases were seen in the concentrations of taurine, aspartate, glutamate, glycine, 1-methyl histidine, isoleucine and arginine. Rather smaller yet significant elevations could be observed in the levels of cystein, threonine, serine, citrulline, methionine and leucine. The only amino acid to show a lowered concentration was alpha-aminobutyrate. Most of the alterations induced by fasting were similar to those in healthy volunteers. An exception was the levels of taurine, which evidenced in RA patients a further increase during starvation, not observed in healthy volunteers, and valine which exhibited, a smaller increment than that apparent in healthy controls. The increase in sulphur-containing amino acids might be interpreted as a sign of an enhanced glutathione (GSH) catabolism, whereas the differing metabolic behaviour of branched chain amino acids (BCAA) suggests a specific reaction of valine in RA disease, similar to that in other catabolic diseases.

Author(s): Gerber DA

Title: **Decreased concentration of freehistidine in serum in rheumatoid arthritis, an isolated amino acidabnormality not associated with generalized hypoaminoacidemia.**

Source: J Rheumatol (JOURNAL OF RHEUMATOLOGY)
1975 Dec; 2 (4): 384-92 Journal Code:JWX

Abstract: The serum concentrations of 12 free amino acids (alanine, arginine, glycine, histidine, isoleucine, leucine, lysine, phenylalanine, serine, threonine, tyrosine, and valine) were measured in 26 patients with rheumatoid arthritis and in 12 control subjects. Patients with rheumatoid arthritis had a low serum histidine concentration (P equals 0.002) but no abnormality of any other amino acid concentration or of the combined concentration of the measured amino acids, excluding histidine. These data and 22 other reported studies provide strong evidence for the presence of hypohistidemia, not associated with generalized hypoaminoacidemia, in patients with rheumatoid arthritis. (J Rheumatol 2: 384-392, 1975).

NEUROLOGY

Author: Barinaga, M
Title: **Learning by diffusion: Nitric oxide may spread memories**.
Source: Nature, 263 (1994) 466..

Author: Bukrinsky, MI; Nottet, HS; et.al.
Title: **Regulation of nitric oxide synthase activity in human immunodeficiency virus type 1 (HIV-1) - Infected monocytes: Implications for HIV-associated neurological disease**.
Source: Journal of Experimental Medicine (1995) 735-745.

Author: Gally, JA; Montague, PR; et al
Title: **The NO hypothesis: possible effects of a short-lived, rapidly diffusible signal in the development and function of the nervous system**.
Source: Proceedings of the National Academy of Sciences, (USA), 87(1990) 3547-3551).

Author: Hoffman, MI
Title: **A new role for gases: Neurotransmission.**.
Source: Science, 252 (1991) 1788.

Author(s):
Odetti P ; Garibaldi S ; Norese R ; Angelini G ; Marinelli L ; Valentini S ; Menini S ; Traverso N ; Zaccheo D ; Siedlak S ; Perry G ; Smith MA ; Tabaton M
Address: Department of Internal Medicine, University of Genoa, Italy.

Title:
Lipoperoxidation is selectively involved in progressivesupranuclear palsy.

Source:
J Neuropathol Exp Neurol (JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTALNEUROLOGY) 2000 May; 59 (5): 393-7 Journal Code: JBR

Abstract:
Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by extensive neurofibrillary tangle (NFT) formation and neuronal loss in selective neuronal populations. Currently, no clues to the biological events underlying the pathological process have emerged. In Alzheimer disease (AD), which shares with PSP the occurrence of NFTs, advanced glycation end products (AGEs) as well as oxidation adducts have been found to be increased in association with neurofibrillary pathology The presence and the amount of lipid and protein oxidation markers, as well as of pyrraline and pentosidine. 2 major AGEs, was assessed by biochemical, immunochemical, and immunocytochemical analysis in midbrain tissue from 5 PSP cases, 6 sporadic AD cases, and 6 age-matched control cases. The levels of 4-hydroxynonenal (HNE) and thiobarbituric acid reactive substances (TBARS), 2 major products of lipid peroxidation, were significantly increased by 1.6-fold ($p < 0.04$) and 3.9-fold ($p < 0.01$), respectively, in PSP compared with control tissues, whereas in AD only TBARS were significantly increased. In PSP tissue the intensity of neuronal HNE immunoreactivity was proportional to the extent of abnormal aggregated tau protein. The amount of protein oxidation products and AGEs was instead similar in PSP and control tissues. In AD, a higher but not significant level of pyrraline and pentosidine was measured, whereas the level of carbonyl groups was doubled. These findings indicate that in PSP, unlike in AD, lipid peroxidation is selectively associated with NFT formation. The intraneuronal accumulation of toxic aldehydes may contributeto hamper tau degradation, leading to its aggregation in the PSP specific abnormal filaments.

7004-12-8 (Arginine)

Author(s):
Xu M ; Ng YK ; Leong SK
Address: Department of Anatomy, Faculty of Medicine, The National University of Singapore, 10 Kent Ridge Crescent, Singapore, 119260.

Title:
Neuroprotective and neurodestructive functions of nitricoxide after spinal cord hemisection.

Source:
Exp Neurol (EXPERIMENTAL NEUROLOGY) 2000 Feb; 161 (2): 472-80

Abstract:
Nitric oxide (NO) may subserve different functions in different central neurons subjected to axotomy. The difference may depend on whether the neurons basally express neuronal nitric oxide synthase (nNOS), a biosynthetic enzyme of NO. This is supported by our previous finding that suggests the differential role of NO in neurons of nucleus dorsalis (ND) and red nucleus (RN) which have different basal expression of nNOS. This study aimed to establish firmly the functions of NO, as revealed by nNOS immunoreactivity and nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) histochemistry, by the administration of endogenous NO donor, l-arginine (l-arg), and NOS inhibitor, l-N(G)-nitroarginine methyl ester (l-NAME). To relate the role of NO to glutamate receptors (GluR), the distributions of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and N-methyl-d-aspartate receptor (NMDAR) in the two nuclei were revealed by immunohistochemical techniques. nNOS immunoreactivity was void in ND neurons, but expressed weakly in the RN normally. It was induced in ipsilateral ND neurons and upregulated on both sides of RN after spinal cord hemisection. Neuronal loss in the ipsilateral ND was augmented by l-arg, but reduced by l-NAME. In the contralateral RN, l-arg attenuated neuronal loss. NMDAR1 was present in most neurons in ND. After axotomy, some NMDAR1 immunoreactive neurons of the ipsilateral ND were induced to express NOS, whereas RN neurons showed strong staining for NMDAR1 and all the AMPA subunits. Most of the NOS-positive neurons in the RN were coexistent with GluR2 in normal rats and those subjected to axotomy. The present data demonstrated that NO exerted neurodestructive function in the non-NOS-containing ND neurons characterized by NMDAR as the predominant glutamate receptor. NO might be beneficial to the NOS-containing RN neurons. This could be attributed to the presence of GluR2. Possible diverse synthesizing pathways of NO in two different central nuclei were suggested from the observation that NOS was colocalized with NADPH-d in ND neurons, but not in RN neurons. Copyright 2000 Academic Press.

Author(s):
Jonakait GM ; Wen Y ; Wan Y ; Ni L
Address: Department of Biological Sciences, Rutgers University, Newark, New Jersey, 07102, USA.

Title:
Macrophage cell-conditioned medium promotes cholinergic differentiation of undifferentiated progenitors and synergizes with nerve growth factor action in the developing basal forebrain.

Source:
Exp Neurol (EXPERIMENTAL NEUROLOGY) 2000 Jan; 161 (1): 285-96

Abstract:
Conditioned medium from stimulated microglia and from the monocyte/macrophage cell line (RAW 264.7; MC-CM) promotes the differentiation of cholinergic neurons

from undifferentiated progenitors in the septal nuclei and adjacent basal forebrain (BF). We have studied the regulation of this process by measuring the activity of choline acetyltransferase (ChAT) in cultured BF taken from embryonic day 16 rat brain. Inhibition of either xanthine oxidase with allopurinol or nitric oxide synthase with N(G)-monomethyl-l-arginine produces a small but significant improvement in the efficacy of MC-CM while inclusion of pyrrolidine dithiocarbamate, a hydroxyl radical scavenger widely used as an antioxidant, lowers MC-CM-induced ChAT activity. Addition of nerve growth factor (NGF) but not brain-derived neurotrophic factor or glial-derived neurotrophic factor together with MC-CM has a synergistic effect on both ChAT activity and ChAT mRNA, raising ChAT activity as much as 29-fold and ChAT mRNA almost 15-fold. While MC-CM raised mRNA for trkA, the effect was not synergistic with NGF. mRNA for the common neurotrophin receptor (p75NTR) showed a modest synergistic increase. Blockade of the Ras/Raf/ERK [extracellular signal-regulated kinase, also known as mitogen-activated protein [(MAP) kinase] signal transduction pathway with either PD28059 (an inhibitor of MAP kinase/ERK kinase kinase or MEK) or N-acetyl-S-farnesyl-l-cysteine (an inhibitor of Ras farnesylation and, hence, activation) inhibited the action of MC-CM. Moreover, a subpopulation of cells responded rapidly to MC-CM with an increased appearance of phosphorylated ERK. Because NGF also utilizes this pathway, synergy may occur along this signal transduction pathway.

Author(s):
D'Hooge R ; Marescau B ; Qureshi IA ; De Deyn PP
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Title:
Impaired cognitive performance in ornithine transcarbamylase-deficient mice on arginine-free diet.

Source:
Brain Res (BRAIN RESEARCH) 2000 Sep 8; 876 (1-2): 1-9

Abstract:
Sparse-fur (spf) mice are a model for the congenital deficiency of ornithine transcarbamylase (OTC), the most common inborn error of urea synthesis in man. In this study, performance of clinically stable spf and control mice (8-10-weeks-old) on two learning tests was assessed under normal Arg(+) or arginine-free Arg(-) diet conditions. Used as an indicator of the metabolic status of the animals, plasma ammonia concentrations were significantly higher in spf than in controls on normal diet, and increased even more during the Arg(-) diet episode. Behaviourally, we found no difference in passive avoidance learning between control and spf mice on Arg(+) diet, whereas in spf mice receiving Arg(-) diet during training, retention performance was significantly reduced. In the hidden-platform water maze, spf mice on Arg(+) diet only showed decreased swimming velocity compared to controls. In mice on Arg(-) diet during the first week of acquisition training, performance on acquisition and retention (probe) trials showed that spf mice experienced more difficulties in actually locating the platform. Visible-platform control experiments only showed a reduction in swimming velocity in spf mice on either diet. We conclude that cognitive performance is impaired in spf mice as a consequence of Arg(-) diet-induced neurochemical alterations.

Author(s):
Hong SJ ; Hwang JH
Address: Department of Pharmacology, Kaohsiung Medical University, Taiwan.
Title:
Reduction of neuronal damage in ischemic stroke usinga combination therapy of TMB-8 with L-arginine.
Source:
Kaohsiung J Med Sci (Kaohsiung J Med Sci) 2000 Apr; 16 (4): 170-80
Abstract:
Treatment with a combination of a calcium antagonist TMB-8 and NO donors, L-arginine and N alpha-benzoyl-L-arginine ethyl ester (BAEE) to prevent experimental ischemic stroke were studied in rats through the permanent occlusion of the middle cerebral artery and common carotid artery for 60 minutes. When the animals were treated with TMB-8, L-arginine, BAEE or NO synthetase inhibitor, nitro-L-arginine at time 0 of ischemia, the areas of neuronal necrosis were reduced by 98%, 99%, 99% and 89%, respectively. When these compounds were administered at 6 hrs after ischemia, the areas of neuronal necrosis were reduced by 91%, 96%, 86% and 81%, respectively. When TMB-8, L-arginine, BAEE or nitro-L-arginine were administered at 24 hours after ischemia, the necrosis areas were reduced less effectively by 80%, 89%, 77% and 60%, respectively. A combination with TMB-8 and L-arginine at time 0, 6 or 24 hr after ischemia resulted in the areas of necrosis being reduced by 99%, 99%, and 89%, respectively. Treatment with the combination of TMB-8 and BAEE at time 0, 6 or 24 hrs after ischemia, resulted in the areas of necrosis being reduced by 99%, 96%, and 82%, respectively. When the drugs were administered at 0 hr of ischemia, L-arginine, BAEE and nitro-L-arginine increased NO synthase activity in the ischemic cortex from 369 +/- 27 of ischemic control to 614 +/- 39, 511 +/- 32 and 406 +/- 16 respectively 1 days after stroke. TMB-8 was a potent agent in reducing intracellular calcium from the base line and blocking the elevation of calcium induced by KCl. The spectrin proteolysis protein, a calcium-activated proteolysis protein was also inhibited by TMB-8 in the ischemic cortex. These results indicated that a combination of TMB-8 and L-arginine is more effective in treating ischemic stroke by simultaneously reducing calcium-activated proteolysis and improving of cerebral blood flow than using TMB-8 or L-arginine alone.

Author(s):
Bath FJ ; Butterworth RJ ; Bath PM
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Title:
Nitric oxide donors (nitrates), L-arginine, or nitricoxide synthase inhibitors for acute ischaemic stroke.
Source:
Cochrane Database Syst Rev (Cochrane Database Syst Rev) 2000; (2): CD000398
Abstract:
BACKGROUND: Nitric oxide has several effects that may be beneficial in ischaemic stroke and useful in the management of hypertension in acute stroke. Some forms of nitric oxide synthase inhibition may also be beneficial. However,

high concentrations of nitric oxide are likely to be toxic to brain tissue. OBJECTIVES: The objective of this review was to assess the effects of nitric oxide donors, L-arginine, or nitric oxide synthase-inhibitors in people with acute ischaemic stroke. SEARCH STRATEGY: We searched the Cochrane Stroke Group trials register (July 1997), Medline (for trials from 1965), Embase (from 1980) and ISI (from 1981). We contacted drug companies and researchers in the field. SELECTION CRITERIA: Randomised and quasi-randomised trials comparing nitric oxide donors, L-arginine, or nitric oxide synthase-inhibitors in patients within one week of onset of confirmed ischaemic stroke. DATA COLLECTION AND ANALYSIS: Two reviewers independently applied the inclusion criteria. MAIN RESULTS: No completed trials were found. One small placebo-controlled trial of glyceryl trinitrate patches is underway. REVIEWER'S CONCLUSIONS: There is currently no evidence from randomised trials on the effects of nitric oxide donors, L-arginine, or nitric oxide synthase-inhibitors in patients with acute ischaemic stroke.

Author(s):
Kidd GA ; Dobrucki LW ; Brovkovych V ; Bohr DF ; Malinski T
Address: Department of Physiology, University of Michigan, Ann Arbor, USA.
Title:
Nitric oxide deficiency contributes to large cerebral infarct size.
Source:
Hypertension (HYPERTENSION) 2000 May; 35 (5): 1111-8
Abstract:
The purpose of this study was to examine the role played by a deficit in nitric oxide (NO) in contributing to the large cerebral infarcts seen in hypertension. Cerebral infarction was produced in rats by occlusion of the middle cerebral artery (MCA). Studies were performed in Sprague-Dawley (SD) rats subjected to NO synthase blockade (N(G)-nitro-L-arginine [L-NNA], 20 mg x kg(-1) x d(-1) in drinking water) and in spontaneously hypertensive stroke-prone rats (SHRSP). NO released in the brain in response to MCA occlusion was monitored with a porphyrinic microsensor in Wistar-Kyoto rats. The increment in NO released with MCA occlusion was 1.31+/-0.05 micromol/L in L-NNA-treated rats, 1.25+/-0.04 micromol/L in SHRSP, 2. 24+/-0.07 micromol/L in control SD rats, and 2.25+/-0.06 micromol/L in Wistar-Kyoto rats ($P<0.0001$ for control versus the other groups). Infarct sizes in the L-NNA-treated and control SD rats were 8.50+/-0. 8% and 5.22+/-0.7% of the brain weights, respectively ($P<0.05$). The basilar arterial wall was significantly thicker in L-NNA-treated rats compared with their controls. We conclude that both the deficit in NO and the greater wall thickness contribute to the larger infarct size resulting from MCA occlusion in SHRSP and in L-NNA-treated rats compared with their respective controls.

Author(s):
Beccaria L ; Marziani E ; Manzoni P ; Arvat E ; Valetto MR ; Gianotti L ; Ghigo E ; Chiumello G
Address: Paediatric Department, University of Milan, Italy.
Title:
Further evidence of cholinergic impairment of the neuroendocrine control of the GH secretion in Down's syndrome.
Source:
Dement Geriatr Cogn Disord (DEMENTIA AND GERIATRIC COGNITIVE DISORDERS) 1998 Mar-Apr; 9 (2): 78-81

Abstract:

There are data indicating that cholinergic activity is precociously impaired in Down's syndrome (DS). On the other hand, acetylcholine as well as arginine (ARG) play a major stimulatory role in the neural control of growth hormone (GH) secretion in humans, likely acting via the inhibition of hypothalamic somatostatin release. The aim of the present study was to verify the effects of pyridostigmine (PD, 120 mg p.o.), a cholinesterase inhibitor, and ARG (0.5 g/kg i.v.) on the growth hormone-releasing hormone (GHRH) (1 microgram/kg i.v.)-induced GH rise in 15 adult patients with DS (M/F: 8/7; age 26.5 +/- 2.2 years; body mass index, BMI: 25.7 +/- 1.0 kg/m2) in which the potentiating effect of PD on GH secretion has been reported to be reduced. The results in DS were compared to those in 15 normal subjects (NS) (M/F: 8/7; age: 30.0 +/- 1.3 years; BMI: 21.4 +/- 0.4 kg/m2). Basal GH and insulin growth factor I (IGF-1) levels in DS (1.8 +/- 0.7 and 206.5 +/- 21.0 micrograms/l) were similar to those in NS (1.4 +/- 0.3 and 179.4 +/- 11.0 micrograms/l). The GH response to GHRH alone in DS (526.5 +/- 120.1 micrograms/l/h) was lower ($p < 0.05$) than that recorded in NS (895.4 +/- 153.7 micrograms/l/h). The GHRH-induced GH rise was potentiated by PD both in DS (1,138 +/- 184.2 micrograms/l/h; $p < 0.02$ vs. GHRH alone) and in NS (2,213.8 +/- 212.8 micrograms/l/h; $p < 0.005$ vs. GHRH alone); however, as the percent potentiating effect of PD was similar in both groups (215 and 247%, respectively) the GH response to GHRH + PD in DS was lower ($p < 0.005$) than that in NS. The GHRH-induced GH rise was also potentiated by ARG in both DS (2,243 +/- 362.4 micrograms/h; $p < 0.001$ vs. GHRH alone) and NS (2,764.3 +/- 325.7 micrograms/l/h; $p < 0.005$ vs. GHRH alone). As the percent potentiating effect of ARG in DS was more marked than in NS (425 vs. 308%, respectively), the GH response to GHRH + ARG became similar in both groups. No sex-related difference was found in the GH response to various stimuli both in DS and NS. In conclusion, these data demonstrate that the potentiating effect of PD but not that of ARG is impaired in adults with DS in whom a reduced somatotrope responsiveness to GHRH is present. These findings indicate that in DS the pituitary GH releasable pool is fully preserved while an impairment of the tuberoinfundibular cholinergic pathways could lead to somatostatinergic hyperactivity and low somatotrope responsiveness to GHRH.

Author(s):
Mochizuki Y ; Oishi M ; Hara M ; Takasu T
Address: Department of Neurology, Nihon University School of Medicine, Tokyo, Japan.

Title:

Amino acid concentration in dementia of the Alzheimer type and multi-infarct dementia.

Source:
Ann Clin Lab Sci (ANNALS OF CLINICAL AND LABORATORY SCIENCE) 1996 May-Jun; 26 (3): 275-8

Abstract:

Amino acids were measured in nine cases of dementia of the Alzheimer type, 10 cases of multi-infarct dementia, and 10 healthy controls. The severity of dementia was examined using mini-mental state test (MMST). Amino acid analysis (41 kinds) in the cerebrospinal fluid (CSF) and serum was performed in the Special Reference Laboratories. In the dementia of the Alzheimer type group, methionine and alanine concentrations in the CSF were significantly increased, and the CSF/serum ratios for both the alanine and glycine

concentrations were significantly increased, in comparison with the healthy control group. In the multi-infarct dementia group, glycine, methionine, threonine, phenylalanine, and citrulline concentrations in the CSF were all higher than in the healthy control group. Significant negative correlations were found between the MMST score and the alanine, urea, arginine, and alpha-aminobutyric acid concentrations in the CSF. The number of amino acids which exhibited abnormality in dementia of the Alzheimer type and multi-infarct dementia was greater in the present study than in previous reports.

Author(s):
Kuiper MA ; Visser JJ ; Bergmans PL ; Scheltens P ; Wolters EC
Address: Department of Neurology, Free University Hospital, Amsterdam, The Netherlands.

Title:
Decreased cerebrospinal fluid nitrate levels in Parkinson's disease, Alzheimer's disease and multiple system atrophy patients.

Source:
J Neurol Sci (JOURNAL OF THE NEUROLOGICAL SCIENCES) 1994 Jan; 121 (1): 46-9

Abstract:
Nitric oxide (NO) is a recently discovered endogenous mediator of vasodilatation, neurotransmission, and macrophage cytotoxicity. NO is thought to have a function in memory and in long-term potentiation. At high concentrations NO is neurotoxic and may play a role in neurodegeneration. NO is formed from L-arginine by the enzyme NO synthase (NOS), for which tetrahydrobiopterin (BH4) is a necessary co-factor. Alzheimer's disease (AD) and, to a lesser degree, Parkinson's disease (PD) are thought to be associated with increased microglial activity, suggesting that NO production may be increased. Alternatively, in circumstances of reduced levels of intracellular L-arginine or BH4, NO production is diminished and neurotoxic oxygen radicals may be produced. Since BH4 is decreased in AD and PD brains, these diseases may be associated with decreased NO production. We investigated these two alternatives by measuring the NO degradation products nitrite and nitrate in cerebrospinal fluid (CSF) of PD (n = 103), AD (n = 13), and multiple system atrophy (MSA; n = 14) patients and controls (n = 20). We found for all patient groups, compared with controls, significantly decreased levels of nitrate, but not nitrite. This finding seems to indicate a decreased NO production of the central nervous system (CNS) in these neurodegenerative disorders.

Author(s):
Ghigo E ; Nicolosi M ; Arvat E ; Marcone A ; Danelon F ; Mucci M ; Franceschi M ; Smirne S ; Camanni F
Address: Department of Clinical Pathophysiology, University of Turin, Italy.

Title:
Growth hormone secretion in Alzheimer's disease: studies with growth hormone-releasing hormone alone and combined with pyridostigmine or arginine.

Source:
Dementia (DEMENTIA) 1993 Nov-Dec; 4 (6): 315-20 Journal Code: BUU
Additional Info: SWITZERLAND

Standard No:
ISSN: 1013-7424

Language:
ENGLISH
Abstract:
There is evidence that GH secretion is reduced in normal elderly subjects as well as in patients with Alzheimer's disease (AD). To clarify the mechanisms underlying this GH hyposecretory state in 14 elderly subjects (age 65-75 years) and 15 AD patients (age 61-78 years), we studied the effects of both pyridostigmine (PD, 120 mg orally), a cholinesterase inhibitor, and arginine (ARG, 0.5 g/kg i.v.), two substances likely acting via inhibition of hypothalamic somatostatin, on GH response to GHRH (1 microgram/kg i.v.). The GH response to PD alone was also studied. Twenty-two young healthy volunteers were studied as control group. Basal GH levels were similar in young, elderly and AD subjects (0.7 +/- 0.2, 0.8 +/- 0.2 and 0.9 +/- 0.2 microgram/l). IGF-I levels were lower ($p < 0.005$) in elderly (73.9 +/- 8.2 microgram/l) and in AD subjects (108.0 +/- 5.9 micrograms/l) than in young subjects (288.7 +/- 22.1 micrograms/l); however, they were higher ($p < 0.01$) in AD patients than in the elderly subjects. The PD-induced GH release did not significantly differ in young, elderly and AD subjects while the GH responses to GHRH in the elderly (AUC: 297.9 +/- 49.2 micrograms/l) and in AD subjects (437.6 +/- 93.5 micrograms/l/h) were lower ($p < 0.01$) than in young subjects (658.6 +/- 100.1 micrograms/l/h). PD potentiated the GH response to GHRH both in elderly and in AD subjects (901.7 +/- 222.4 and 1,070.3 +/- 207.2 micrograms/l/h, $p < 0.005$) but these responses were lower ($p < 0.0001$) than those recorded in young subjects (2,041.1 +/- 245.6 micrograms/l/h).(ABSTRACT TRUNCATED AT 250 WORDS)

Author(s):
Tohgi H ; Takahashi S ; Abe T
Address: Department of Neurology, Iwate Medical University, Morioka, Japan.
Title:
The effect of age on concentrations of monoamines, amino acids, and their related substances in the cerebrospinal fluid.
Source:
J Neural Transm Park Dis Dement Sect (JOURNAL OF NEURAL TRANSMISSION. PARKINSONS DISEASE AND DEMENTIA SECTION) 1993; 5 (3): 215-26
Abstract:
We studied age-related changes in the concentrations of monoamines, amino acids, and their related substances in the cerebrospinal fluid on 144 neurologically normal subjects. The concentrations of tyrosine, 3-O-methyldopa, dopamine (total), norepinephrine (total), homovanillic acid, p-hydroxyphenylacetic acid, and 5-hydroxytryptophan increased significantly with age ($p < 0.05$), and the concentration of 3.4-dihydroxyphenylacetic acid displayed a non-significant trend to decrease, whereas concentrations of other monoamine precursors and metabolites were unchanged. We found the significant positive correlations between the concentrations of HVA and 5-HIAA ($p < 0.001$), between tyrosine and tryptophan ($p < 0.001$), and between tyrosine and 3-O-methyldopa ($p < 0.001$). The concentrations of asparagine, glycine, taurine, and alanine increased significantly with age ($p < 0.05$), while glutamine, arginine, and threonine concentrations did not change with age. The aspartate, glutamate, and GABA concentrations displayed the non-significant trends to decrease in the elderly subjects. The concentrations of aspartate, glutamate, and GABA had mutually significant positive correlations ($p < 0.05$),

but had significant negative correlations with the concentrations of some neutral amino acids. The urate and xanthine concentrations increased significantly with age ($p < 0.01$). These findings suggest that the concentrations of monoamine and amino acid transmitters and their related compounds in the cerebrospinal fluid reflect age-related changes in the synthesis, release, and reuptake mechanisms of the transmitters and their transport mechanisms across the blood-brain barrier.

Author(s): Kuiper MA ; Teerlink T ; Visser JJ ; Bergmans PL ; Scheltens P ; Wolters EC
Address: Department of Neurology, Free University Hospital, Amsterdam, The Netherlands.
Title: **L-glutamate, L-arginine and L-citrulline levels in cerebrospinal fluid of Parkinson's disease, multiple system atrophy, and Alzheimer's disease patients.**
Source: J Neural Transm (JOURNAL OF NEURAL TRANSMISSION) 2000; 107 (2): 183-9
Abstract: Alterations in neuronal nitric oxide (NO) production may play a role in the pathophysiology of Parkinson's disease (PD) Alzheimer's disease (AD), and multiple system atrophy (MSA). The biosynthesis of NO is dependent on the availability of L-arginine, the substrate for NO-synthase (NOS), and on L-glutamate, which stimulates NO synthesis via the NMDA receptor. In this process L-citrulline is formed. We measured the levels of these amino acids in cerebrospinal fluid (CSF) of 108 PD patients, 12 AD patients, 15 MSA patients and 21 healthy subjects. A slight but statistically significant elevation of CSF L-citrulline was found in MSA patients, while CSF L-glutamate was found to be significantly decreased in AD patients. We found no significant changes in L-arginine levels. Although the relation between the CSF levels of these amino acids and neuronal NO production is still unclear, our findings suggest that AD is associated with a decrease in NO synthesis.

Author(s): Shinde UA ; Mehta AA ; Goyal RK
Address: Department of Pharmacology, L M College of Pharmacy, Navrangpura, Ahmedabad, India.
Title: **Nitric oxide: a molecule of the millennium.**
Source: Indian J Exp Biol (INDIAN JOURNAL OF EXPERIMENTAL BIOLOGY) 2000 Mar; 38 (3): 201-10
Abstract: Recognition of Nitric oxide (NO) as the chemical entity of endothelium-derived relaxing factor (EDRF) has renewed the interest of the scientific community in the last decade. The outcome of research the world over is that the dreaded environmental pollutant is found to be a fundamental physiological mediator and effector. NO is synthesized endogenously by enzymes nitric oxide synthase (NOS) in specialized tissues from its precursor L-arginine. The L-arginine-NO

biosynthetic pathway is involved in physiological processes such as vasodilation, memory, neuroprotection, peristalsis, penile erection, immune defense, various endocrine and exocrine secretions in various systems such as cardiovascular, CNS, reproductive and immune system. Small quantities of NO produced by constitutive enzymes mediate these physiological effects. The expression of inducible enzyme or overstimulation of constitutive enzymes leading to production of large quantities of NO is implicated in the cytotoxic effects observed in various disorders like AIDS, cancer, Alzheimer's, arthritis etc. In conclusion, NO is a 'double edged sword' and the challenge before the scientific community is to develop strategies for using it to our advantage.

Author(s): Ghosh C ; Lahiri DK
Address: Institute of Psychiatric Research, Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202, USA.
Title: **Increased vulnerability of neuronal cell lines to sodium nitroprusside-mediated toxicity is caused by the decreased level of nitric oxide metabolites.**
Source: J Mol Neurosci (JOURNAL OF MOLECULAR NEUROSCIENCE) 1999 Aug-Oct; 13 (1-2): 77-92
Abstract: Nitric oxide (NO) is an unstable radical produced during the oxidative deamination catalyzed by NO synthase (NOS) that converts L-arginine to L-citrulline. NO is also generated nonenzymatically from a group of compounds, called NO donors, such as sodium nitroprusside (SNP). NO directly or through its metabolites has been implicated in several disorders, including Alzheimer's disease (AD). Since NO is a highly labile unstable free gas, we measured the stable end products, nitrite and nitrate (NOx). Here, we investigated the effect of SNP-mediated NO release in different cell types and its effect on the beta-amyloid precursor protein (betaAPP). When different cell types were induced with SNP, a significant level of NOx was detected in a time and dose-dependent manner over the spontaneous release of NOx by SNP. The astrocytes, glial, and epithelial cell lines released significantly higher level of NOx as compared to neuronal cells following the exposure of SNP. The latter group of cells was more sensitive to NO-mediated cytotoxicity, as demonstrated by the lactate dehydrogenase assay. The SNP-mediated toxicity is known to be caused by the accumulation of cyanide ions and we report that the ability of cells to protect against it depends on the levels of nitric oxide metabolites. Cell lines, such as astrocytic and epithelial, that

produce more NOx are better protected against the SNP-induced toxicity than the less NOx-protecting neuronal cell lines. The possibility of differential susceptibility of neurons and astrocytes resulting from the different content of reduced glutathione is also discussed. The release of NOx was prevented by cotreatment with a NO scavenger and superoxide dismutase but not by a NOS inhibitor. The activity of NOS was decreased when cytosolic extracts were incubated with SNP. In the conditioned medium of SNP-induced cells, the level of soluble betaAPP (sAPP) was decreased, and this decrease was more apparent in neuronal than astrocytic cell lines. Taken together, these results suggest that the SNP-derived NO release is independent of the NOS pathway, that various cell types metabolize SNP differently, and that neuronal cell lines are more vulnerable with SNP treatment with lowered sAPP secretion. Since the neuronal cell lines lack a nitric-oxide-generated protective mechanism, we speculate that these cells may be the first targets of neurodegeneration by several toxic agents, including the cyanides and peroxynitrites.

Author(s): Lahiri DK ; Ghosh C
Address: Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202-4887, USA. DLAHIRI@IUPUI.EDU
Title: **Interactions between melatonin, reactive oxygen species, and nitric oxide.**
Source: Ann N Y Acad Sci (ANNALS OF THE NEW YORK ACADEMY OF SCIENCES) 1999; 893: 325-30
Abstract: Accumulation of reactive oxygen species is critical for the neuropathology of Alzheimer's disease. Melatonin hormone, an antioxidant, could play a key role in aging and senescence. Nitric oxide, a biologically active unstable radical, is synthesized by nitric oxide synthase when converting L-arginine to L-citrulline. We have investigated whether the treatment of cultured cells with melatonin could possibly reduce the release of free radicals and other ROS. We assayed NO indirectly by measuring the level of its stable end products, nitrite/nitrate (NOx), using the Griess reagent. When the neuroblastoma cells such as N1E-115 were treated with a NO donor such as sodium nitroprusside (SNP), a significant level of NOx was detected in a time- and dose-dependent manner in the conditioned medium compared to the untreated cells or SNP-containing media. In neuroblastoma cells, the release of NOx as mediated by SNP was significantly inhibited by treatment with (i) carboxy-PTIO, a NO scavenger; (ii) SOD-1, superoxide dismutase; and (iii) melatonin. In these cells SNP-mediated NOx release was mediated by superoxide ions and/or free radicals that can be inhibited by melatonin. The ROS-scavenging function of melatonin along with its neuroprotective and neurodifferentiating role can be utilized for the prevention of neurodegenerative disorders such as AD.

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Charles Flahault, 34060, Montpellier, France.
Title: **Neurodegenerative disorders: the role of peroxynitrite.**
Source: Brain Res Brain Res Rev (BRAIN RESEARCH. BRAIN RESEARCH REVIEWS) 1999 Aug; 30 (2): 153-63
Abstract: Inflammatory reaction is thought to be an important contributor to neuronal damage in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and the parkinsonism dementia complex of Guam. Among the toxic agents released in brain tissues by activated cells, we focus attention in this review on peroxynitrite, the product of the reaction between nitric oxide (NO) and superoxide. Peroxynitrite is a strong oxidizing and nitrating agent which can react with all classes of biomolecules. In the CNS it can be generated by microglial cells activated by pro-inflammatory cytokines or beta-amyloid peptide (beta-A) and by neurons in three different situations: hyperactivity of glutamate neurotransmission, mitochondrial dysfunction and depletion of L-arginine or tetrahydrobiopterin. The first two situations correspond to cellular responses to an initial neuronal injury and the peroxynitrite formed only exacerbates the inflammatory process, whereas in the third situation the peroxynitrite generated directly contributes to the initiation of the neurodegenerative process.

Author(s): Blum-Degen D ; Heinemann T ; Lan J ; Pedersen V ; Leblhuber F ; Paulus W ; Riederer P ; Gerlach M
Address: Clinical Neurochemistry, University of WŸrzburg, FŸchsleinstrasse 15, D-97080, Wurzburg, Germany.
Title: **Characterization and regional distribution of nitric oxide synthase in the human brain during normal ageing.**
Source: Brain Res (BRAIN RESEARCH) 1999 Jul 10; 834 (1-2): 128-35 Journal Code: B5L
Abstract: Nitric oxide (NO) is a highly diffusible cellular mediator generated from L-arginine by the enzyme nitric oxide synthase (NOS). As little is known about the regional distribution of NOS in the human brain, we examined the distribution pattern of nitric oxide synthase activity in 28 regions of the human brain using the [(3)H]L-citrulline formation assay. To elucidate which isoforms contribute to the total NOS activity we performed Western blot analysis of neuronal, inducible and endothelial NOS. We further determined brain levels of arginine and citrulline as a potential index of NOS activity pre mortem. NOS activity appears to remain unaltered during ageing and is independent of post

mortem delay, gender or sample storage time. We identified a regional pattern of NOS distribution with highest levels of NOS activity in the substantia innominata, cerebellar cortex, nucleus accumbens and subthalamicus, whereas lowest levels were measured in the corpus callosum, thalamus, occipital cortex, and dentate nucleus. nNOS was measured throughout the brain, in contrast iNOS and eNOS were not detectable. We therefore conclude that primarily nNOS is responsible for NOS activity in the human brain. Levels of citrulline were higher than those of arginine, but did not correlate with the enzyme activity, suggesting that these parameters are unsuitable for testing NOS activity premortem. The characterization and topographical pattern of NOS in the human brain during normal ageing may assist our understanding of the physiological role of NO and its relevance in Parkinson's and Alzheimer's disease, alcoholism, schizophrenia and AIDS. Copyright 1999 Elsevier Science B.V.

PSYCHIATRY

Author(s): Griffiths J ; Ravindran AV ; Merali Z ; Anisman H
Address: Department of Psychiatry, University of Ottawa, Ottawa, Canada.
Title: **Dysthymia: a review of pharmacological and behavioral factors.**
Source: Mol Psychiatry (MOLECULAR PSYCHIATRY) 2000 May; 5 (3): 242-61
Abstract: Although dysthymia, a chronic, low-grade form of depression, has a morbidity rate as high as that of major depression, and increases the risk for major depressive disorder, limited information is available concerning the etiology of this illness. In the present report we review literature concerning the biological and characterological features of dysthymia, the effectiveness of antidepressant treatments, the influence of stressors in the precipitation and maintenance of the disorder, and both quality of life and psychosocial correlates of the illness. We also provisionally suggest that dysthymia may stem from disturbances of neuroendocrine and neurotransmitter functioning (eg, corticotropin releasing hormone and arginine vasopressin within the hypothalamus, or alternatively monoamine variations within several extrahypothalamic sites), and may also involve cytokine activation. The central disturbances may reflect phenotypic variations of neuroendocrine processes or sensitization of such mechanisms. It is suggested that chronic stressor

experiences or stressors encountered early in life lead to the phenotypic neurochemical alterations, which then favor the development of the dysthymic state. Owing to the persistence of the neurochemical disturbances, vulnerability to double depression is increased, and in this instance treatment with antidepressants may attenuate the symptoms of major depression but not those of the basal dysthymic state. Moreover, the residual features of depression following treatment may be indicative of underlying neurochemical disturbances, and may also serve to increase the probability of illness recurrence or relapse.

Author(s): ElgŸn S ; Kumbasar H
Address: University of Ankara, Faculty of Medicine, Department of Biochemistry, Turkey.
Title: **Increased serum arginase activity in depressed patients.**
Source: Prog Neuropsychopharmacol Biol Psychiatry (PROGRESS IN NEURO-PSYCHOPHARMACOLOGY AND BIOLOGICAL PSYCHIATRY) 2000 Feb; 24 (2): 227-32
Abstract: 1. Arginase, an important part of the arginine-regulating system modulates nitric oxide generation; a neuroregulatory agent, which has been implicated in various neuropathological conditions. 2. In this regard, the authors investigated the arginine-nitric oxide pathway by measuring serum arginase activity in drug free major (n=18) and minor depressed outpatients (n=12) and healthy control subjects (n=30) in order to make a contribution to the understanding of disease mechanism. 3. Major depressed patients were found to have significantly higher serum arginase activity compared to controls ($p<0.001$) and minor depressives ($p=0.001$). Moreover, there was significant positive correlation between arginase activity and severity of depression in patients ($p<0.001$). 4. Results suggest that the arginine-nitric oxide pathway is involved in depression. Enhanced arginase activity in major depressed patients possibly leading to a decrease in nitric oxide synthesis may contribute to the symptomatology of depression.

Author(s): Gianotti L ; Arvat E ; Valetto MR ; Ramunni J ; Di Vito L ; Maccagno B ; Camanni F ; Ghigo E
Address: Department of Internal Medicine, University of Turin, Italy.
Title:
Effects of beta-adrenergic agonists and antagonists on the growth hormone response to growth hormone-releasing hormone in anorexia nervosa.

Source: Biol Psychiatry (BIOLOGICAL PSYCHIATRY) 1998 Feb 1; 43 (3): 181-7

Abstract: BACKGROUND: In anorexia nervosa (AN), growth hormone (GH) hypersecretion and low insulin-like growth factor I (IGF-I) levels are present. It is unclear whether this is due to a peripheral GH resistance and a reduced IGF-I negative feedback on GH secretion or to a primary hypothalamic dysfunction. In AN, in contrast to normal subjects, cholinergic antagonists and agonists, whose action is somatostatin (SS)-mediated, have reduced and absent effects on the GH response to growth hormone-releasing hormone (GHRH). Since arginine, another substance acting via inhibition of SS, maintains its potentiating effect on GH secretion in AN, it has been hypothesized that somewhat specific alteration of the SS-mediated cholinergic influence may be present in this condition. To further clarify the neural control of AH secretion in AN, we evaluated the effects of beta-adrenergic agonists and antagonists, which are known to inhibit and increase, respectively, the GHRH-induced GH secretion in normal subjects. METHODS: We studied the effect of atenolol (ATE), a beta 1-adrenergic antagonist, and salbutamol (SALB), a beta 2-adrenergic agonist, on the GHRH-induced GH release in 10 patients with AN and in 10 normal age-matched women (NW). RESULTS: Basal GH levels were higher, whereas IGF-I were lower in AN than in NW. The GHRH-induced GH rise in AN was higher than that in NW. ATE significantly enhanced the GH response to GHRH in NW, but not in AN. The GH responses to GHRH after ATE pretreatment were similar in NW and in AN. The GH response to GHRH was inhibited by SALB in both NW and AN. The GH responses to GHRH after SALB pretreatment were similar in NW and AN. CONCLUSIONS: These data reveal an exaggerated somatotrope responsiveness to GHRH in AN that is not further increased by beta-adrenergic blockade, while is abolished by beta-adrenergic activation. This suggests that an impairment of beta-adrenergic influence on GH secretion is present in anorexia nervosa.

Mark:

Author(s): Melis MR ; Argiolas A

Address: B.B. Brodie Department of Neuroscience, University of Cagliari, Italy.

Title: **Role of central nitric oxide in the control of penile erection and yawning.**

Source: Prog Neuropsychopharmacol Biol Psychiatry (PROGRESS IN NEURO-PSYCHOPHARMACOLOGY AND BIOLOGICAL PSYCHIATRY) 1997 Aug; 21 (6): 899-922

Abstract:

1. Recent experimental evidence has shown that nitric oxide (NO) plays an important role in the expression of penile erection and yawning and that this molecule has to be added to the list of the best known neurotransmitters and neuropeptides involved in this symptomatology. 2. This was first suggested by the ability of NO synthase inhibitors injected in the lateral ventricles (i.c.v.) or in the paraventricular nucleus of the hypothalamus (PVN) to prevent these behavioral responses induced by dopamine agonists, oxytocin and NMDA. The inhibitory effect of NO synthase inhibitors was not observed when these compounds were injected concomitantly with L-arginine, the precursor of NO. Most important, this hypothalamic nucleus is one of the richest brain areas of NO synthase and also the brain site where dopamine, NMDA and oxytocin act to induce penile erection and yawning by activating central NO synthase containing oxytocinergic neurons. 3. NO synthase inhibitors given i.c.v. but not in the PVN prevent also penile erection and yawning induced by ACTH and serotonin1c agonists, which induce these responses by acting with mechanisms unrelated to oxytocinergic transmission. 4. Dopamine agonists, NMDA and oxytocin increase NO production in the PVN at doses that induce penile erection and yawning, as determined by measuring the concentration of NO2- and NO3- in the dialyzate obtained with a vertical probe implanted in the PVN by in vivo microdialysis. 5. NO donors, such as nitroglycerin, sodium nitroprusside and hydroxylamine, induce penile erection and yawning indistinguishable from those induced by oxytocin, dopamine agonists or NMDA when injected in the PVN. The NO donor response was prevented by the i.c.v. injection of the oxytocin receptor antagonist d(CH2)5-Tyr(Me)-Orn8-vasotocin, indicating that these compounds also induce penile erection and yawning by activating oxytocinergic transmission. 6. Finally, guanylate cyclase inhibitors (i.e. methylene blue and LY 83583) and hemoglobin injected in the PVN do not prevent drug-induced penile erection and yawning, nor 8-Br-cGMP injected in the PVN induces these behavioral responses suggesting that the mechanism by means of which endogenous or NO donor-derived NO facilitates oxytocinergic transmission to induce penile erection and yawning is not related to the activation of guanylate cyclase. Furthermore, since hemoglobin, in spite of its ability to prevent drug-induced NO production in the PVN, does not prevent penile erection and yawning, it is likely that NO acts as an intracellular rather than an

intercellular modulator in the PVN neurons in which is formed to facilitate the expression of these behavioral responses.

Author(s): Du W ; Harvey JA
Address: Department of Pharmacology, Medical College of Pennsylvania, Philadelphia, USA.
Title: **The nitric oxide synthesis inhibitor L-NAME facilitates associative learning.**
Source: Prog Neuropsychopharmacol Biol Psychiatry (PROGRESS IN NEURO-PSYCHOPHARMACOLOGY AND BIOLOGICAL PSYCHIATRY) 1996 Oct; 20 (7): 1183-95
Abstract: 1. Nitric oxide has been suggested to play an important role in synaptic plasticity and in learning. 2. The authors examined the effects of NW-nitro-L-arginine methyl ester, a competitive and enantiomeric specific inhibitor of nitric oxide synthase, on classical conditioning of the rabbit's nictitating membrane response. 3. It was found that L-NAME significantly enhanced the acquisition of conditioned responses. 4. The enhanced conditioned responses were not due to a sensitization of the conditioned and unconditioned reflexes or to changes in baseline levels of responding. 5. The dose and route of administration of L-NAME employed in this study had no effect on blood pressure. 6. These results suggest that nitric oxide normally functions as a tonic inhibitory modulator of associative learning and that procedures aimed at decreasing its production may provide a novel approach for improving learning.

Author(s): Ghigo E ; Arvat E ; Gianotti L ; Nicolosi M ; Valetto MR ; Avagnina S ; Bellitti D ; Rolla M ; MŸller EE ; Camanni F
Address: Department of Clinical Pathophysiology, University of Turin, Italy.
Title: **Arginine but not pyridostigmine, a cholinesterase inhibitor, enhances the GHRH-induced GH rise in patients with anorexia nervosa.**
Source: Biol Psychiatry (BIOLOGICAL PSYCHIATRY) 1994 Nov 15; 36 (10): 689-95
Abstract: Pirenzepine, a muscarinic antagonist probably acting via stimulation of hypothalamic somatostatin release, abolishes the growth hormone releasing hormone (GHRH)-stimulated growth hormone (GH) rise in normal subjects but only blunts it in patients with anorexia nervosa (AN). This finding suggested the existence in AN of an alteration of cholinergic system and/or somatostatinergic tone. To further investigate these mechanisms, in 11 AN women patients (age 18.8 +/- 0.9 years; BMI 13.4 +/- 0.4) we studied the GH response alone (1 microgram/Kg IV

as a bolus at 0 min) and combined with pyridostigmine (PD, 120 mg orally, 60 min before GHRH administration), a cholinesterase inhibitor, or arginine (ARG 30 g infused over 30 min starting at 0 min), two compounds probably acting via inhibition of hypothalamic somatostatin (SS) release. The GH response to GHRH preceded by a previous (120 min before) neurohormone administration also was studied. All these tests also were performed in 20 normal age-matched women (age 22.0 +/- 1.8 yrs; BMI20.1 +/- 2.4). Basal serum GH levels were higher in AN patients than in normal volunteers (NV) (10.3 +/- 3.4 versus 2.8 +/- 0.3 microgram/L; $p < 0.001$), whereas plasma IGF-I levels were lower in AN patients than in NV (43.3 +/- 10.6 versus 172.4 +/- 13.9 micrograms/L; $p < 0.00001$). In AN patients, GHRH administration induced a GH rise higher, though not significantly, than that in NV [delta area under the curve (AUC) 1173.6 +/- 167.6 versus 834.6 +/- 188.1 micrograms/L/h]. The GH response to the second of two consecutive GHRH boluses was lower ($p < 0.01$) than that of the first one either in AN patients or in NV (67.6 +/- 27.4 and 53.1 +/- 25.7 micrograms/L/h, respectively).(ABSTRACT TRUNCATED AT 250 WORDS)

Author(s): Kaye WH ; Gwirtsman HE ; George DT
Address: University of Pittsburgh, School of Medicine, Department of Psychiatry, Western Psychiatric Institute and Clinic, PA 15212.
Title: **The effect of bingeing and vomiting on hormonal secretion.**
Source: Biol Psychiatry (BIOLOGICAL PSYCHIATRY) 1989 Mar 15; 25 (6): 768-80
Abstract: Women who are of normal weight and have bulimia nervosa have multiple neuroendocrine disturbances. The reasons for these neuroendocrine abnormalities are not known, but there are reasons to suspect that bingeing and vomiting behavior could be contributory. It is well known that food consumption in healthy volunteers increases plasma insulin, cortisol, and prolactin secretion and suppresses growth hormone secretion, whereas activation of the emetic reflex increases plasma arginine vasopressin (AVP) secretion. The purpose of this study was to investigate the effects of bingeing and vomiting on these hormones. In comparison with healthy control women consuming a large meal, bulimic patients, when bingeing and vomiting, had an exaggerated secretion of either the amount and/or the duration of insulin, cortisol, and prolactin. Vasopressin secretion was

not increased during or after bingeing and vomiting, probably because bulimic subjects do not become nauseated. In addition, bulimic patients had significantly reduced baseline plasma prolactin and possibly elevated baseline cortisol compared with controls. In summary, this study supports the presence of neuroendocrine disturbances in bulimia and raises a question as to whether or not excessive and prolonged food consumption (and/or vomiting) are contributory.

GASTROENTEROLOGY AND HEPATOLOGY

Author(s): Straathof JW ; Adamse M ; Onkenhout W ; Lamers CB ; Masclee AA
Address: Department of Gastroenterology-Hepatology, Leiden University Medical Center, The Netherlands.
Title: **Effect of L-arginine on lower oesophageal sphincter motility in man.**
Source: Eur J Gastroenterol Hepatol (EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY) 2000 Apr; 12 (4): 419-24 Journal Code: B9X
Additional Info: ENGLAND
Standard No: ISSN: 0954-691X
Language: ENGLISH
Abstract: OBJECTIVE: Inhibitory responses of the lower oesophageal sphincter (LOS) are mediated via an L-arginine/nitric oxide (NO) pathway. L-arginine is known as the precursor of NO. We have studied the effect of intravenous L-arginine on LOS motility in man. DESIGN: Twelve healthy subjects participated in a double-blind, placebo-controlled randomized study. METHODS: We investigated the effect of continuous infusion of L-arginine (500 mg/kg body weight/120 min) in six subjects under fasting conditions. Six other subjects were studied under postprandial conditions. LOS pressure (LOSP), swallow-induced LOS relaxations and transient lower oesophageal sphincter relaxations (TLOSR) were measured with sleeve manometry combined with pH metry. The meal consisted of a carbohydrate-high fat meal. Blood samples were taken before and after administration of L-arginine or saline to determine plasma levels of amino acids, cholecystokinin and gastrin. RESULTS: Plasma levels of arginine and citrulline significantly ($P < 0.05$) increased during L-arginine infusion. L-arginine did not affect plasma hormone levels. Under fasting conditions, LOSP and TLOSR were not influenced by L-arginine. Ingestion of the carbohydrate-high fat meal significantly decreased LOSP. L-arginine did not significantly influence TLOSR frequency, either

under fasting conditions or postprandially.
CONCLUSIONS: These results suggest that in humans under fasting or postprandial conditions intravenous infusion of L-arginine does not influence LOS motility.

Author(s): Efron D ; Barbul A
Address: Department of Surgery, Sinai Hospital of Baltimore, MD 21215, USA.
Title: **Role of arginine in immunonutrition.**
Source: J Gastroenterol (JOURNAL OF GASTROENTEROLOGY) 2000; 35 Suppl 12: 20-3
Abstract: Arginine plays an important role in many physiologic and biologic processes beyond its role as a protein-incorporated amino acid. Dietary supplementation of arginine can enhance wound healing, regulate endocrine activity and potentiate immune activity. Under normal unstressed conditions the arginine requirement of adult humans is fulfilled by endogenous sources, however this is compromised during times of stress, especially in critical illness. These finding have led to use of arginine supplementation as part of an immune-enhancing dietary regimen to help combat the immune suppression seen in such patients. Though the results from studies examining the use of this type of immunonutrition in critically ill patients are far from definitive, they are promising that this mode of therapy may be of some advantage. A better understanding of the in vivo biology of arginine and its metabolism is necessary to truly define a benefit from arginine supplementation.

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Title: **Regulatory mechanism of acid secretion in the damaged stomach: role of endogenous nitric oxide.**
Source: J Gastroenterol Hepatol (JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY) 2000 Mar; 15 Suppl: D37-45 Journal Code: A6J
Additional Info: AUSTRALIA
Standard No: ISSN: 0815-9319
Language: ENGLISH
Abstract: The present article overviews the regulatory mechanism of acid secretion in the stomach after damage with taurocholate (TC), one of the bile acids. Mucosal exposure of a rat stomach to 20 mmol/L TC for 30 min caused a decrease of acid secretion with a concomitant increase in nitric

oxide (NO) and prostaglandin (PG) E2 (PGE2) as well as Ca2+ in the luminal contents. Prior administration of N(G)-nitro-L-arginine methyl ester (L-NAME), as well as indomethacin, significantly attenuated the reduction of acid secretion by TC and acid secretion was even increased in the presence of L-NAME. The acid stimulatory effect of L-NAME in the damaged stomach was not mimicked by aminoguanidine and was antagonized by co-administration of L-arginine but not D-arginine. Increased NO release in the damaged stomach was suppressed by pretreatment with L-NAME or co-application of EGTA and the latter also inhibited the increase in luminal Ca2+. The enhanced acid secretory response in the presence of L-NAME was also inhibited by cimetidine, FPL-52694 (a mast cell stabilizer) or sensory deafferentation. Mucosal exposure to TC caused an increase in luminal histamine output, together with a decrease in the number of mucosal mast cells in the stomach. These changes were prevented by FPL-52694 and sensory deafferentation and were also partly suppressed by indomethacin. In addition, the acid stimulatory action of L-NAME in the damaged stomach was significantly mitigated when indomethacin was administered together with L-NAME. We conclude that: (i) damage in the stomach may activate acid a stimulatory pathway in addition to a PG-, NO- and Ca2+-dependent inhibitory mechanism, but the latter effect overcomes the former, resulting in a decrease in acid secretion; (ii) acid stimulation in the damaged stomach is mediated by histamine released from the mucosal mast cell, a process interacting with capsaicin-sensitive sensory nerves; (iii) the increase in luminal Ca2+ plays a role in increasing NO production and, hence, in regulating acid secretion; and (iv) PG may have a dual role in the regulation of acid secretion in the damaged stomach: an inhibitory effect at the parietal cell and an excitatory effect, probably through enhancing the release of mucosal histamine.

Author(s): Tomita R ; Tanjoh K ; Fujisaki S ; Fukuzawa M
Address: First Department of Surgery, Nihon University School of Medicine, Japan.
Title: **The role of nitric oxide (NO) in the human pyloric sphincter**.
Source: Hepatogastroenterology (HEPATO-GASTROENTEROLOGY) 1999 Sep-Oct; 46 (29): 2999-3003
Abstract: BACKGROUND/AIMS: Nitric oxide (NO) has recently been shown to be a neurotransmitter in non-adrenergic non-cholinergic (NANC) inhibitory

nerves in the gastrointestinal tract. To clarify the role of NO in the human pyloric sphincter, enteric nerve responses in pyloric tissue specimens obtained from patients with gastric cancer were investigated. METHODOLOGY: Fresh specimens of normal pylorus obtained from 18 patients with gastric cancer were used. The subjects consisted of 12 men and 6 women, aged from 45-74 years (average: 60.1 years). A mechanograph was used to evaluate in vitro pyloric sphincter muscle responses to electrical field stimulation (EFS) of adrenergic and cholinergic nerves before and after treatment with various autonomic nerve blockers, and N(G)-nitro-L-arginine (L-NNA) and L-arginine. RESULTS: Cholinergic nerves were mainly involved in the regulation of enteric nerve responses to EFS in the basal condition of the study, and NANC inhibitory nerves acted on human pylorus. L-NNA concentration dependently inhibited the relaxation in response to EFS in the human pylorus, and this inhibitory effect in the pylorus was reversed by L-arginine. CONCLUSIONS: These findings suggest that the cholinergic/adrenergic and NANC inhibitory nerves play important roles in regulating contraction and relaxation of the human pylorus, and that NO plays an important role as a neurotransmitter in NANC inhibitory nerves of the human pylorus.

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Address: First Department of Surgery, Nihon University School of Medicine, Tokyo, Japan.
Title: **Physiological studies on nitric oxide in the right sided colon of patients with diverticular disease.**
Source: Hepatogastroenterology (HEPATO-GASTROENTEROLOGY) 1999 Sep-Oct; 46 (29): 2839-44
Abstract: BACKGROUND/AIMS: Previously, we reported that non-adrenergic non-cholinergic (NANC) inhibitory nerves are decreased in the left-sided colon of patients with diverticular disease, contributing to their intraluminal high pressure by segmentation (1). It is established that nitric oxide (NO) is released by stimulation of NANC inhibitory nerves. Among Oriental people, including the Japanese, right-sided diverticular disease has predominated more frequently than among Western people. In order to evaluate the function of NO in the right-sided colon of patients with diverticular disease, we examined the enteric nerve responses in colonic materials from patients with this disease, using the right-sided normal colon as a control. METHODOLOGY: Colonic tissue specimens were obtained from 8 patients with diverticular disease of the

right-sided colon, and normal segments of the right-sided colon were obtained from 11 patients with localized diseases. A mechanograph was used to evaluate in vitro colonic responses to electrical field stimulation (EFS) of adrenergic and cholinergic nerves before and after treatment with various autonomic nerve blockers, N(G)-nitro-L-arginine (L-NNA), and L-arginine. RESULTS: 1) Cholinergic nerves were more dominant in the diverticular colon than in the normal colon ($p<0.01$). 2) NANC inhibitory nerves were found to act on the normal colon and to a lesser extent in the diverticular colon ($p<0.05$). 3) NO mediates the relaxation reaction of NANC inhibitory nerves in the normal colon and to a lesser extent in the diverticular colon. CONCLUSIONS: The intrinsic intestinal innervation contains excitatory and inhibitory nerves and the former, especially cholinergic nerves, are dominant in the right-sided colon with diverticula. In addition, reduction of the action of NANC inhibitory nerves by substances such as NO may be largely related to the tight intraluminal pressure by colonic segmentation observed in the right-sided colon with diverticula.

Author(s): Jurkowska G ; Rydzewska G ; Gabryelewicz A ; Dzieciol J
Address: Gastroenterology Department, University Medical School, Bialystok, Poland.
Title: **The role of nitric oxide in caerulein-induced acute pancreatitis and the recovery process after inflammatory damage.**
Source: Eur J Gastroenterol Hepatol (EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY) 1999 Sep; 11 (9): 1019-26 Journal Code: B9X
Additional Info: ENGLAND
Standard No: ISSN: 0954-691X
Language: ENGLISH
Abstract: OBJECTIVES: Nitric oxide (NO) is involved in the control of pancreatic blood flow and secretion, and its role in the maintenance of pancreatic tissue has been suggested. The aim of our study was to evaluate the influence of NO on pancreatic trophic parameters during acute pancreatitis induction and the pancreas recovery process. DESIGN/METHODS: Acute pancreatitis was induced in rats by a supramaximal dose of caerulein. During acute pancreatitis induction, rats were treated with L-arginine (a substrate for NO synthesis), glyceryl trinitrate (NTG, NO donor), glycine, N(G)-nitro-L-arginine (L-NNA, NO synthase inhibitor), L-arginine + L-NNA, or saline. Pancreatic weight, total contents of RNA, DNA,

protein, amylase and chymotrypsin as well as pancreas histology and the number of proliferating acinar cells were evaluated after pancreatitis induction in all groups and additionally after 7 and 14 days of recovery in untreated acute pancreatitis rats or those injected with L-NNA and/or L-arginine. RESULTS: Pancreas destruction after acute pancreatitis was evidenced by similar decreases of all parameters in untreated acute pancreatitis rats or those treated with L-NNA or glycine when compared to control healthy animals. The recovery process after acute pancreatitis was not affected by L-NNA injections; however, the increased cell proliferation occurred later than in untreated rats. NTG and especially L-arginine treatment resulted in significant attenuation of pancreas damage (partially prevented by L-NNA treatment) as evidenced by biochemical data with a slight improvement in morphology. Treatment with L-arginine alone or in combination with L-NNA resulted in augmented cell proliferation after acute pancreatitis induction followed by earlier recovery in comparison to untreated acute pancreatitis rats or the L-NNA-injected group. CONCLUSION: The present study suggests the involvement of NO in mild acute pancreatitis and in the recovery process after inflammatory damage.

Author(s): Ueda T ; Sakabe T ; Oka M ; Maeda Y ; Nishida M ; Murakami F ; Maekawa T
Address: Department of Anesthesiology-Resuscitology, Yamaguchi University School of Medicine, Ube, Japan.
Title: **Decreased hepatic nitric oxide synthesis during liver surgery.**
Source: Hepatogastroenterology (HEPATO-GASTROENTEROLOGY) 1999 May-Jun; 46 (27): 1917-22
Abstract: BACKGROUND/AIMS: Liver cells can produce nitric oxide from L-arginine through the action of nitric oxide synthase, but local changes in the concentrations of nitric oxide-related metabolites during liver surgery are not well characterized. We investigated such changes during and after liver surgery. METHODOLOGY: We determined nitrite plus nitrate, L-arginine and L-citrulline concentrations in radial arterial and hepatic venous blood during and after liver surgery in 17 patients. Portal venous blood concentrations were also measured at the end of surgery in 7 patients. RESULTS: Both arterial and hepatic venous nitrite plus nitrate concentrations were significantly decreased during surgery and remained low compared to pre-operative values until post-operative day 2. Arterial and hepatic venous nitrite plus nitrate concentrations

were not significantly different. L-arginine concentrations in both arterial and hepatic venous blood were significantly decreased during surgery, but returned to pre-operative levels on post-operative day 1. L-arginine concentrations in hepatic venous blood were significantly lower than in arterial blood. L-citrulline concentrations in both arterial and hepatic venous blood were significantly decreased during surgery compared to pre-operative values, and tend to be decreased until post-operative day 2. L-citrulline concentrations were significantly higher in hepatic venous blood than in arterial blood. CONCLUSIONS: Hepatic nitric oxide production was decreased peri-operatively during liver surgery. The decreases in L-arginine concentrations and in nitric oxide synthase activity may account for the decrease in nitric oxide production.

Author(s): Tanaka N ; Tanaka K ; Nagashima Y ; Kondo M ; Sekihara H
Address: Third Department of Internal Medicine, Yokohama City University School of Medicine, Yokohama, Japan.
Title: **Nitric oxide increases hepatic arterial blood flow in rats with carbon tetrachloride-induced acute hepatic injury**.
Source: Gastroenterology (GASTROENTEROLOGY) 1999 Jul; 117 (1): 173-80
Abstract: BACKGROUND & AIMS: Little is known about the changes in hepatic blood flow associated with acute hepatic injury. The aim of this study was to investigate the effect of nitric oxide (NO) on hepatic blood flow and the severity of hepatic injury in rats with carbon tetrachloride (CCl_4)-induced acute hepatic injury. METHODS: Rats were pretreated with CCl_4 to induce acute hepatic injury. Hepatic blood flow was measured using a radioactive microsphere method. The role of NO in the regulation of hepatic blood flow and the severity of hepatic injury was investigated by administering NG-nitro-L-arginine (L-NNA) and aminoguanidine (AG). Plasma nitrite/nitrate levels, hepatic NO synthase (NOS) activity, and expression of hepatic NOS messenger RNA (mRNA) were measured, and histological examinations were performed. RESULTS: Hepatic arterial and portal venous blood flow was increased significantly by CCl_4, without any change in mean arterial pressure or cardiac output. L-NNA and AG dose-dependently decreased hepatic arterial blood flow, with the highest dose resulting in complete blockade of hepatic arterial dilation, but failed to change portal venous blood flow. Histologically, administration of AG

aggravated the hepatic injury in CCl4-treated rats. Plasma nitrite/nitrate levels and hepatic NOS activity were increased significantly by CCl4 treatment. Inducible NOS mRNA was detected in CCl4-treated rats but not in the controls. CONCLUSIONS: The results of this study suggest that the increased hepatic arterial blood flow in CCl4-induced acute hepatic injury is mediated by excessive NO production and up-regulated by inducible NOS, which plays a role in reducing hepatic injury.

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Title: **Nitric oxide prevents tumor necrosis factor alpha-induced rat hepatocyte apoptosis by the interruption of mitochondrial apoptotic signaling through S-nitrosylation of caspase-8.**
Source: Hepatology (HEPATOLOGY) 2000 Oct; 32 (4 Pt 1): 770-8 Journal Code: GBZ
Additional Info: UNITED STATES
Standard No: ISSN: 0270-9139
Language: ENGLISH
Abstract: Mitochondrial cytochrome c release plays a critical role in apoptotic signal cascade after the activation of cell surface death receptors. We investigated the role played by nitric oxide (NO) in mitochondrial apoptotic signaling in tumor necrosis factor alpha (TNF-alpha) plus actinomycin D (TNF-alpha/ActD)-induced apoptosis. NO produced either by S-nitroso-N-acetyl-DL-penicillamine (SNAP) or inducible NO synthase (iNOS) prevented TNF-alpha/ActD-induced apoptosis in hepatocytes and also inhibited both caspase-8-like (IETDase) and caspase-3-like protease (DEVDase) activity as well as mitochondrial cytochrome c release. Recombinant human (rh) caspase-8 induced the cleavage of the cytochrome c-effluxing factor Bid and cytochrome c release from purified mitochondria in the reconstitution system with Bid(+/+) cytosol, but not with Bid(-/-) cytosol. The addition of SNAP and the caspase-8 inhibitor Ac-IETD-fmk inhibited caspase-8-dependent Bid cleavage and cytochrome c release. The inhibitory effect of NO on caspase-8 was reversed by dithiothreitol (DTT). Furthermore, rh-caspase-8 was found to be modified by S-nitrosylation with 1.7 moles of NO bound per mole of enzyme. Treatment of hepatocytes with interleukin 1beta (IL-1beta) plus interferon gamma

(IFN-gamma), which induced iNOS expression and NO production, suppressed TNF-alpha/ActD-induced Bid cleavage and mitochondrial cytochrome c release. The NOS inhibitor N(G)-monomethyl-L-arginine (NMA) inhibited the protective effects of IL-1beta and IFN-gamma. The liver-specific NO donor V-PYRRO/NO also inhibited in vivo elevation of IETDase activity, Bid cleavage, and mitochondrial cytochrome c release in the livers of rats injected with TNF-alpha plus D-galactosamine. Our results indicate that one mechanism by which NO protects hepatocytes from TNF-alpha/ActD-induced apoptosis is via the interruption of mitochondrial apoptotic signaling through S-nitrosylation of caspase-8.

Author(s): Jurkowska G ; Rydzewska G ; Gabryelewicz A ; Dzieciol J
Address: Gastroenterology Department, University Medical School, Bialystok, Poland.
Title: **The role of nitric oxide in caerulein-induced acute pancreatitis and the recovery process after inflammatory damage.**
Source: Eur J Gastroenterol Hepatol (EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY) 1999 Sep; 11 (9): 1019-26 Journal Code: B9X
Additional Info: ENGLAND
Standard No: ISSN: 0954-691X
Language: ENGLISH
Abstract: OBJECTIVES: Nitric oxide (NO) is involved in the control of pancreatic blood flow and secretion, and its role in the maintenance of pancreatic tissue has been suggested. The aim of our study was to evaluate the influence of NO on pancreatic trophic parameters during acute pancreatitis induction and the pancreas recovery process. DESIGN/METHODS: Acute pancreatitis was induced in rats by a supramaximal dose of caerulein. During acute pancreatitis induction, rats were treated with L-arginine (a substrate for NO synthesis), glyceryl trinitrate (NTG, NO donor), glycine, N(G)-nitro-L-arginine (L-NNA, NO synthase inhibitor), L-arginine + L-NNA, or saline. Pancreatic weight, total contents of RNA, DNA, protein, amylase and chymotrypsin as well as pancreas histology and the number of proliferating acinar cells were evaluated after pancreatitis induction in all groups and additionally after 7 and 14 days of recovery in untreated acute pancreatitis rats or those injected with L-NNA and/or L-arginine. RESULTS: Pancreas destruction after acute pancreatitis was evidenced by similar decreases of all parameters in untreated acute pancreatitis rats or those treated with L-NNA or

glycine when compared to control healthy animals. The recovery process after acute pancreatitis was not affected by L-NNA injections; however, the increased cell proliferation occurred later than in untreated rats. NTG and especially L-arginine treatment resulted in significant attenuation of pancreas damage (partially prevented by L-NNA treatment) as evidenced by biochemical data with a slight improvement in morphology. Treatment with L-arginine alone or in combination with L-NNA resulted in augmented cell proliferation after acute pancreatitis induction followed by earlier recovery in comparison to untreated acute pancreatitis rats or the L-NNA-injected group. CONCLUSION: The present study suggests the involvement of NO in mild acute pancreatitis and in the recovery process after inflammatory damage.

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Address: First Department of Surgery, Kansai Medical University, Moriguchi, Osaka, Japan.
Title: **An enhancement of nitric oxide production regulates energy metabolism in rat hepatocytes after a partial hepatectomy.**
Source: J Hepatol (JOURNAL OF HEPATOLOGY) 1999 May; 30 (5): 944-50
Abstract: BACKGROUND/AIMS: Infection after a liver resection often results in hepatic failure. Nitric oxide is one of the candidates which has been suspected to cause cellular dysfunction during infection in the liver. We have previously reported that the inflammatory cytokine interleukin-1beta (IL-1beta) induced the expression of the inducible nitric oxide synthase gene in primary cultured rat hepatocytes. We hypothesized that an enhancement of nitric oxide production after the resection was implicated in a change in liver energy metabolism, thus resulting in liver dysfunction. METHODS: In this study, we performed a 70% hepatectomy or a sham operation in rats, and then isolated hepatocytes from the remnant liver by collagenase perfusion. The cultured hepatocytes were treated with cytokines including IL-1beta. The effects on nitric oxide induction, the ATP content and ketone body ratio (acetoacetate/beta-hydroxybutyrate) were then compared between the partial hepatectomized (PH) and sham-operated (control) rats. RESULTS: IL-1beta augmented the induction of nitric oxide production two-fold in hepatocytes from the PH rats as compared to the control rats. IL-1beta markedly decreased the ATP content in the PH rats, although

IL-1beta also decreased the ATP content in the control rats, but to a lesser extent. IL-1beta also decreased the ketone body ratio in both groups. The addition of L-arginine further stimulated the inhibition of the ATP levels and the ketone body ratio concomitantly with increased nitric oxide production in the PH rats. N(G)-monomethyl-L-arginine, an inhibitor of nitric oxide synthase, abolished the effects of IL-1beta on the ATP levels and ketone body ratio, as well as on the nitric oxide production. CONCLUSIONS: These results demonstrate that the decreased ATP content observed in PH rats resulted from an increase in nitric oxide production. The decrease in ketone body ratio indicates that nitric oxide-induced mitochondrial dysfunction contributes significantly to ATP attenuation in hepatocytes. Therefore, the regulation of nitric oxide induction may be crucial for preventing liver failure after a hepatic resection.

Author(s): Cottart CH ; Do L ; Blanc MC ; Vaubourdolle M ; Descamps G ; Durand D ; Galen FX ; Clot JP
Address: Department of Endocrinology, UFR des Sciences Pharmaceutiques et Biologiques, Universit* Ren* Descartes, Paris, France.
Title: Hepatoprotective effect of endogenous nitric oxide during ischemia-reperfusion in the rat.
Source: Hepatology (HEPATOLOGY) 1999 Mar; 29 (3): 809-13
Abstract: The aim of this study was to evaluate the protective or deleterious effects of endogenous nitric oxide (NO) on liver cells during hepatic ischemia-reperfusion (IR) in the rat. Injury to hepatocytes and endothelial cells was evaluated by determining cytolysis-marker activity in plasma (alanine transaminase [ALT]; aspartate transaminase [AST]) and plasma hyaluronic acid (HA) concentration. Clamping the hepatic pedicle for 45 minutes caused a significant increase in plasma AST and ALT activity after 30 minutes of reperfusion, which reached a maximum (+270% and +740%, respectively) after 6 hours of reperfusion. Plasma HA concentration was significantly higher (+130%) only after 6 hours of reperfusion. Administration of a nonselective NO synthase (NOS) inhibitor, Nomega-nitro-L-arginine (L-NNA; 10 mg/kg iv), 30 minutes before IR, caused marked aggravation of postischemic liver injury, as shown by plasma ALT and AST activity and HA concentration. This deleterious effect was partially prevented by the simultaneous injection of L-arginine, the endogenous NO precursor (100 mg/kg iv). Interestingly, L-arginine alone limited

postischemic damage (AST, -25%; ALT, -45%; HA, -21% vs. untreated IR rats at 6 hours reperfusion). Pretreatment with the Guanosine 3':5'-cyclic monophosphate-independent vasodilator, prazosin, partially reversed L-NNA effects, but it did not protect untreated IR animals. Pretreatment with aminoguanidine, a selective inhibitor of inducible NOS, did not aggravate hepatic IR injury. Thus, endogenous NO, probably produced by an early and transient activation of a constitutive NOS, protects both hepatocytes and endothelial cells against liver ischemia-reperfusion injury, and this effect is not entirely a result of vasorelaxation.

ONCOLOGY

Author: Brittenden, J: Heys, SD; et al
Title: **Dietary supplementation with L-Arginine in patients with breast cancer (>4cm) Receiving multimodal treatment: Report of a feasibility study.**
Source: Brittish Journal of Cancer, 69 (1994) 205-212.

Author: Brittenden, Park KG; J: Heys, SD; et al
Title: **L-Arginine stimulates host defense in patients with breast cancer**.
Source: Surgery (1994) 205-212.

Author: Cho-Chung, YS; Clair, T; et.al
Title: **Growth arrest and morphological change in human breast cancer cells by dibutyryl cyclic AMP and L-Arginine**.
Source: Science, 214 (1981) 77-79.

Author: Keller, R; Geiges, M; et al
Title: **L-arginine-dependent reactive nitrogen intermediates as mediators of tumor cell killing by activated macrophages.**.
Source: Cancer Research, 50 (1990) 1421-1425.

Author: Kubota, A; Meguid, MM; et al
Title: **Amino acid profiles correlate diagnostically with organ sites in three kinds of malignant tumors**.
Source: Cancer, 69 (1992) 2343-2348.

OBSTETRICS/GYNECOLOGY

Author: Helmbrecht, GD; Farhat, MY; et al.
Title: **L-arginine reverses the adverse pregnancy changes induced by nitric oxide**.
Source: American Journal of Obstetrics and Gynecology, 175 (1996) 800-805.

Author(s):
Piccinini F ; Rovati L ; Zanni A ; Cagnacci A ; Volpe A ; Facchinetti F
Address: Department of Obstetric, Gynecologic and Pediatric Science, University of Modena and Reggio Emilia, Italy.
Title:
Indirect evidence that estrogen replacement therapy stimulates nitric oxide synthase in postmenopausal women.

Source:
Gynecol Endocrinol (GYNECOLOGICAL ENDOCRINOLOGY) 2000 Apr; 14 (2): 142-6

Abstract:
The aim of the study was to investigate the effects of estrogen replacement therapy (ERT) on nitric oxide (NO) activity in healthy postmenopausal women. The study group consisted of 22 postmenopausal women (last menses at least 12 months prior to study entry) who were randomized to receive treatment for 2 months with patches that delivered either 50 micrograms/day of 17 beta-estradiol or placebo in a cross-over design. Blood samples for measurements of serum citrulline and arginine were collected at the start of the study and at the end of each treatment course. Serum citrulline and arginine were measured using high-performance liquid chromatography with fluorometric detection. Arginine levels were significantly lower in the ERT group compared to the placebo group, while citrulline levels did not change. The percentage citrulline/arginine ratio was significantly higher in the ERT group (42.9 +/- 21.6) compared to the placebo group (33.9 +/- 18.5) ($p < 0.01$). The citrulline/arginine ratio, both at baseline and during either ERT or placebo administration demonstrated a positive linear correlation with body mass index (BMI). No correlations were found between follicle stimulating hormone, estradiol and insulin levels and BMI. No correlations were found between age, time since menopause and baseline arginine and citrulline levels or the citrulline/arginine ratio. These data indirectly demonstrate that transdermal estradiol replacement in postmenopausal women is able to stimulate NO production through the involvement of endogenous L-arginine. A positive linear correlation was found between BMI and the citrulline/arginine ratio, suggesting an additional protective cardiovascular effect in overweight women.

Author(s): Benedetto C ; Marozio L ; Neri I ; Giarola M ; Volpe A ; Facchinetti F
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Title: **Increased L-citrulline/L-arginine plasma ratio in severe preeclampsia**.

Source: Obstet Gynecol (OBSTETRICS AND GYNECOLOGY) 2000 Sep; 96 (3): 395-9 Journal Code: OC2
Additional Info: UNITED STATES

Standard No: ISSN: 0029-7844

Language: ENGLISH

Abstract: OBJECTIVE: To evaluate nitric oxide (NO) production in patients with pregnancy-induced hypertension or preeclampsia and in controls. METHODS: Four groups of pregnant women were included: 17 patients with pregnancy-induced hypertension, ten with mild or moderate preeclampsia, 17 with severe preeclampsia, and 44 normotensive women matched for weeks of gestation at blood sampling with the cases. Plasma levels of L-citrulline and L-arginine were measured by using high-performance liquid chromatography. RESULTS: The mean plasma levels of L-citrulline and the ratio of L-citrulline to L-arginine, which reflects NO production, were higher in women with severe preeclampsia than in controls, patients with

pregnancy-induced hypertension, and patients with mild or moderate preeclampsia. CONCLUSION: Nitric oxide production is enhanced in severe preeclampsia, possibly as a compensatory phenomenon for the increased synthesis and release of vasoconstrictors and platelet-aggregating agents.

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Address: Department of Medicine IV, University of Erlangen-NŸrnberg, Klinikum NŸrnberg-SŸd, Germany.
Title: **Effects of oral contraceptives on vascular endothelium in premenopausal women.**
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 2000 Jul; 183 (1): 28-33 Journal Code: 3NI
Additional Info: UNITED STATES
Standard No: ISSN: 0002-9378
Language: ENGLISH
Abstract: OBJECTIVE: Premenopausal women are protected against atherosclerosis by high plasma estrogen levels, which have been suggested to augment endothelial nitric oxide synthesis and to improve endothelial function. In contrast, premenopausal use of oral contraceptives is associated with an increased cardiovascular risk. We investigated the influence of oral contraception on endothelial function. STUDY DESIGN: Sixteen healthy premenopausal women with a mean age (+/-SD) of 27 +/- 3 years, 8 of whom used oral contraceptives and 8 of whom did not, were examined in a case-control study. Forearm plethysmography was used to measure changes of forearm blood flow in response to intra-arterial infusion of increasing doses of acetylcholine, sodium nitroprusside, and N (G)-monomethyl-L -arginine. RESULTS: Endothelium-dependent vasodilatation (change from baseline after acetylcholine 48 microg/min) was similar between women with (828% +/- 137%) and without oral contraception (701% +/- 114%; P not significant), as was endothelium-independent vasodilatation (change from baseline after sodium nitroprusside 3200 ng/min, 271% +/- 38% vs 289% +/- 23%; P not significant). In contrast, inhibition of nitric oxide synthase with N (G)-monomethyl-L -arginine induced a significantly more marked decrease in blood flow among women with oral contraception than among those without at all dosages (change from baseline after 4-micromol/min N (G)-monomethyl-L -arginine, -26% +/- 3% vs -14% +/- 5%; P =.009 by analysis of variance). CONCLUSION: Stimulated nitric oxide bioavailability remained unaffected in a group of premenopausal

women receiving oral contraceptives. In contrast, basal nitric oxide production and release appeared to be enhanced by oral contraceptive use.

Author(s): Kublickiene KR ; Lindblom B ; KrŸger K ; Nisell H
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Title: **Preeclampsia: evidence for impaired shear stress-mediated nitric oxide release in uterine circulation.**
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 2000 Jul; 183 (1): 160-6
Abstract: OBJECTIVE: We sought to compare flow-mediated dilatation and myogenic and norepinephrine-induced tone in myometrial resistance arteries from women with preeclampsia and healthy pregnant women and to evaluate the role that nitric oxide may play in these responses. STUDY DESIGN: Arteries (approximately 200 microm, at 50 mm Hg) were dissected from myometrial biopsy specimens from women undergoing emergency cesarean delivery because of preeclampsia (n = 6) and from healthy control subjects undergoing planned cesarean delivery (n = 9). Responses to intraluminal flow, pressure, and a constrictor agonist (norepinephrine, 10(-6) mol/L) were studied in the absence and presence of the nitric oxide synthase inhibitor N omeganitro-L -arginine (10(-4) mol/L). Myogenic and norepinephrine-induced tone were calculated after the determination of artery diameter in the absence of extracellular calcium and in the presence of papaverine (10(-4) mol/L). RESULTS: An increase in intraluminal flow led to dilatation of isolated myometrial arteries from healthy gravid women, whereas flow-mediated dilatation was absent in arteries from gravid patients with preeclampsia (increase in diameter at maximum flow rate of 204 microL/min, 28% +/- 5% in healthy gravid patients vs -15% +/- 6% in gravid women with preeclampsia; analysis of variance, P <.05). Addition of N omega-nitro-L -arginine had no significant effect on flow-mediated responses in arteries from women with preeclampsia, whereas flow-mediated dilatation was abolished after addition of N omega-nitro-L -arginine in arteries from healthy gravid women (increase in diameter at a maximum flow rate of 204 microL/min, 28% +/- 5% control vs -9% +/- 5% N omega-nitro-L -arginine; analysis of variance, P <.05). Arteries from women with preeclampsia developed pressure-induced myogenic and norepinephrine-induced tone, similar

to that obtained in arteries from healthy gravid women. In arteries from gravid women with preeclampsia, inhibition of nitric oxide synthase enhanced myogenic-induced tone (25% +/- 4% control vs 35% +/- 5% N omega-nitro-L -arginine; P <.05) and norepinephrine-induced tone (36% +/- 4% control vs 46% +/- 6% N omega-nitro-L -arginine; P <.05), as in arteries from healthy gravid women. CONCLUSIONS: Nitric oxide may participate in modulation of pressure- and norepinephrine-induced tone even in preeclampsia, but the shear stress-mediated release of nitric oxide is absent. Failure of shear stress-mediated dilation in myometrial arteries from gravid women with preeclampsia might contribute to the impaired uteroplacental blood flow in this disease.

Author(s): Fallucca F ; Sabbatini A ; Di Biase N ; Borrello E ; Napoli A ; Sciullo E
Address: Dipartimento di Scienze Cliniche, Centro Interdipartimentale di Medicina Sociale, Universita La Sapienza, Roma, Italy. fallucca@tin.it
Title: **Fetal pancreatic function in infants of diabetic and rhesus-isoimmunized women.**
Source: Obstet Gynecol (OBSTETRICS AND GYNECOLOGY) 2000 Feb; 95 (2): 195-8 Journal Code: OC2
Additional Info: UNITED STATES
Standard No: ISSN: 0029-7844
Language: ENGLISH
Abstract: OBJECTIVE: To measure insulin and glucagon concentrations in amniotic fluid (AF) collected near term in basal conditions and after an arginine test in diabetic, rhesus-isoimmunized, and control pregnant women. METHODS: At baseline, AF was collected from 44 diabetic, 32 rhesus-isoimmunized, and 27 control pregnant women in late pregnancy. Fifty-two diabetic, six rhesus-isoimmunized, and nine control pregnant women had amniocentesis 2 hours after arginine infusion (30 g intravenous/30 minutes) at 33-36 weeks. RESULTS: Baseline AF glucose concentrations were significantly greater in diabetic women than the other conditions, and they related to the gestational age in the women with hemolytic disease of the newborn. Insulin and glucagon AF content of isoimmunized pregnancies overlapped controls, whereas insulin and insulin/glucagon molar ratios were significantly higher, and glucagon values lower, in diabetic pregnancies compared with isoimmunized and control pregnancies. In isoimmunized pregnancies, the AF concentrations of glucose, insulin, and glucagon were correlated with gestational age (less than 34, 34 weeks or more). The samples collected after

arginine infusion, compared with those collected at baseline, showed significantly greater insulin and insulin/glucagon molar ratio values in diabetic (28 +/- 5 versus 11 +/- 1 microU/mL, P = .001; 29.4 +/- 1.7 versus 12.0 +/- 2.8, P = .001) and in Rh pregnant women (18 +/- 6 versus 7.7 +/- 0.7 microU/mL, P = .001; 30 +/- 9 versus 3.4 +/- 0.4 I/G, P = .001), whereas no significant difference was observed in the controls. CONCLUSION: Basal islet hormone concentrations in AF are modified by maternal diabetes and further influenced by arginine administration. Arginine produces an AF response that is similar in pregnancies complicated by diabetes mellitus and rhesus-isoimmunization, despite different (hyperglycemia and euglycemia) maternal blood glucose levels.

Author(s): Anumba DO ; Ford GA ; Boys RJ ; Robson SC
Address: Department of Obstetrics and Gynaecology, University of Newcastle upon Tyne, United Kingdom.
Title: **Stimulated nitric oxide release and nitric oxide sensitivity in forearm arterial vasculature during normotensive and preeclamptic pregnancy.**
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 1999 Dec; 181 (6): 1479-84
Abstract: OBJECTIVE: We sought to determine whether the enhanced forearm vascular activity of nitric oxide during pregnancy and preeclampsia is associated with altered smooth muscle sensitivity to nitric oxide or with stimulated nitric oxide release. STUDY DESIGN: Forearm blood flow responses to brachial artery infusion of glyceryl trinitrate (a nitric oxide donor), serotonin (an endothelium-dependent nitric oxide-mediated agonist), and ritodrine (a beta-adrenergic receptor agonist) were studied in 10 nonpregnant women, 12 pregnant women, and 7 women with preeclampsia by means of strain-gauge plethysmography. Responses to each drug (maximum dilator response and the sum of the percentage of dilator responses to each drug) were compared by analysis of variance. RESULTS: Compared with nonpregnant women, pregnant subjects showed reduced responses to serotonin (summary response, 117 +/- 19 vs 221 +/- 30; P <.05). Responses to serotonin were reduced in the group with preeclampsia compared with those in the nonpregnant group (summary response, 71 +/- 28; P <.05) but did not differ from the responses in pregnant women. There were no differences between responses to glyceryl trinitrate and responses to ritodrine in any of the groups. CONCLUSION: Vascular smooth muscle sensitivity to nitric oxide is not altered in normal pregnancy or preeclampsia,

but dilator responses to serotonin appear blunted. Alterations in serotonin receptor coupling to nitric oxide synthase, or a limitation of availability of the substrate for nitric oxide synthase (L-arginine) during pregnancy, could account for the reduction in stimulated nitric oxide release.

Author(s): Ronzoni S ; Marconi AM ; Cetin I ; Paolini CL ; Teng C ; Pardi G ; Battaglia FC
Address: Department of Obstetrics and Gynecology, San Paolo Institute of Biomedical Sciences, University of Milan, Italy.
Title: Umbilical amino acid uptake at increasing maternal amino acid concentrations: effect of a maternal amino acid infusate.
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 1999 Aug; 181 (2): 477-83
Abstract: OBJECTIVE: Our purpose was to establish whether, in normal human pregnancies, the maternal intravenous infusion of amino acids can increase fetal amino acid uptake and amino acid concentrations. STUDY DESIGN: Twenty-six normal pregnancies were studied at the time of cesarean delivery (38-40 weeks' gestation). In 10 cases an amino acid formulation (Freamine 8.5% III, Baxter) was infused into a maternal vein before cesarean delivery. Maternal blood samples were obtained during the course of the study. Umbilical venous and arterial samples were obtained from the clamped segment of the cord. There were no differences between the 2 groups for fetal and placental weights and for fetal oxygenation and acid-base balance. RESULTS: Maternal amino acid concentrations increased significantly in the group receiving infusions. Significant increases in umbilical venous concentrations were observed for most amino acids, except for histidine and threonine. The amino acid umbilical arteriovenous differences per mole of oxygen (AA/O(2) ratio) increased significantly for leucine, isoleucine, valine, methionine, phenylalanine, arginine, glycine, serine, alanine, and proline. There were no significant increases for lysine, histidine, and threonine. CONCLUSION: An increase in maternal concentrations leads to an increase in the delivery of most amino acids to the fetus.

Author(s): Weeks AD ; Massmann AG ; Monaghan JM ; Crowther D ; Duffy SR ; Walker JJ ; Figueroa JP
Address: Department of Obstetrics and Gynaecology, Research School of Medicine, Leeds, United Kingdom.
Title: **Decreasing estrogen in nonpregnant women lowers**

uterine myometrial type I nitric oxide synthase protein expression.

Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 1999 Jul; 181 (1): 25-30 Journal Code: 3NI
Additional Info: UNITED STATES
Standard No: ISSN: 0002-9378
Language: ENGLISH
Abstract: OBJECTIVE: Our purpose was to study the effect of estrogen on myometrial nitric oxide synthase. STUDY DESIGN: Twenty-four women were randomly assigned to treatment with gonadotropin-releasing hormone agonist or placebo for 8 weeks before hysterectomy, at which time samples of myometrium were collected and the serum levels of estrogen, nitrate, and nitrite measured. Myometrial nitric oxide synthase was measured with the arginine-citrulline assay. The levels of endothelial nitric oxide synthase and neuronal nitric oxide synthase were determined by Western blot analysis. RESULTS: Myometrial nitric oxide synthase was 88% calcium dependent but only partially calmodulin dependent. Women treated with gonadotropin-releasing hormone agonist had postmenopausal levels of estradiol and had significantly lower levels of myometrial neuronal nitric oxide synthase than those in the control group. Total, endothelial, and inducible nitric oxide synthase levels in the myometrium were unchanged, as were serum nitrite and nitrate levels. CONCLUSION: Neuronal nitric oxide synthase is regulated in the myometrium by estrogen. Myometrial nitric oxide synthase is not all calmodulin dependent; this may represent the activity of a novel nitric oxide synthase isoform.

Author(s): Ekerhovd E ; WeidegŒrd B ; BrSnnstrsm M ; Norstrsm A
Address: Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Gsteborg University, Sweden.
Title: **Nitric oxide-mediated effects on myometrial contractility at term during prelabor and labor.**
Source: Obstet Gynecol (OBSTETRICS AND GYNECOLOGY) 1999 Jun; 93 (6): 987-94
Abstract: OBJECTIVE: To assess the existence of a nitric oxide (NO) system in the human myometrium and the effects of mediators of this system on contractile activity in vitro. METHODS: Myometrial tissue was obtained before the onset of labor and during labor at term. Production of NO was assessed by the use of nicotinamide dinucleotide phosphate diaphorase staining and by immunoblots for NO. Effects of NO were examined by adding L-arginine (the substrate for NO synthesis); N(G)-nitro-L-arginine methyl

ester (an inhibitor of NO synthase); two NO donors, sodium nitroprusside and spermine NONOate; as well as 8-bromo cyclic guanosine monophosphate (8-bromo cGMP) (a second messenger analogue) to organ baths. RESULTS: Myometrial NO production was indicated by positive nicotinamide adenine dinucleotide phosphate diaphorase staining. Immunoblots detected endothelial NO synthase, whereas only a weak signal for inducible NO synthase was seen. The addition of L-arginine (10(-4)-10(-3) mol/L) did not result in any change of contractility. N(G)-nitro-L-arginine methyl ester (10(-3) mol/L) caused a minor increase of contractility in half of the specimens. Sodium nitroprusside, spermine NONOate, and 8-bromo cGMP resulted in a concentration-dependent inhibition of contractility (10(-7)-10(-6) mol/L for sodium nitroprusside, 10(-6)-10(-5) mol/L for spermine NONOate, and 10(-5)-10(-3) mol/L for 8-bromo cGMP). However, at 10(-5)-10(-4) mol/L, sodium nitroprusside exhibited a dose-dependent increase in the frequency of contractions. Women in prelabor did not differ from those in active labor. CONCLUSION: The myometrium produces NO at term. Nitric oxide inhibits myometrial contractile activity. The responsiveness to NO is similar in nonlaboring and laboring women.

Author(s): Egberts J ; van den Bosch N ; Brand R
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Title: Nitric oxide metabolites, cyclic guanosine 3,5 monophosphate and dimethylarginines during and after uncomplicated pregnancies: a longitudinal study.
Source: Eur J Obstet Gynecol Reprod Biol (EUROPEAN JOURNAL OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE BIOLOGY) 1999 Jan; 82 (1): 35-40 Journal Code: E4L
Additional Info: IRELAND
Standard No: ISSN: 0301-2115
Language: ENGLISH
Abstract: OBJECTIVE: In cross-sectional studies, the variability between women may mask or deny gestational changes, related to the nitric oxide-cyclic GMP system. Therefore, we analyzed longitudinally as markers of this system, the urinary levels of nitrite+nitrate (NOx), cyclic guanosine 3',5' monophosphate (cGMP) and of the inhibitor of nitric oxide synthase, dimethylarginine (DMA). STUDY DESIGN: Late-afternoon urine samples were obtained from 20 women with uncomplicated pregnancies and nine non-pregnant women. Creatinine concentrations (mol)

were determined with the Jaff* reagent and NOx (mmol) with the Griess reagent after reduction of nitrate. cGMP (micromol) was determined in an enzyme immunoassay and DMA (mmol) after solid-phase extraction and liquid chromatography. Trend analyses and (paired) t-tests were done for detection of time-related differences. RESULTS: The NOx/creatinine (mmol/mol) ratios of the non pregnant women (63.8+/-18.8, S.D.) did not differ from those of the pregnant women at the onset of pregnancy (70.5+/-36.4). Over the entire pregnancy period these ratios declined significantly (P<0.001) and lower values were found at the end of gestation and after birth (49.6+/-22.4). The cGMP/creatinine (micromol/mol) and DMA/creatinine ratios (mmol/mol) changed parabolically (P<0.001). The maxima of 68.0+/-19.9 and of 4.95+/-1.01 were found at week 20 and 16, respectively. These ratios declined to 45.2+/-17.7 and to 4.03+/-0.83 at the end of gestation but not further during parturition (39.6+/-17.2 and 4.01+/-1.90). The lowest cGMP/creatinine ratios occurred one month after birth (27.4+/-15.7) while in the non-pregnant women the value was 15.3+/-6.2 microM/M. The lowest DMA/creatinine ratios, measured one month after birth (3.41+/-1.28 mmol/mol) were similar to those of the non-pregnant women (3.75+/-0.39 mmol/mol). Positive instead of negative relationships were found between the DMA results and those of the cGMP (P<0.001) and NOx determinations (P<0.05). CONCLUSIONS: (1) The gestational changes of the urinary NOx/creatinine and especially of the GMP/creatinine ratio reflect most likely changes in vascular resistance. (2) Because of the variability of the results between but also within women, these ratios are useless to monitor supposed changes in NO production during parturition.

Author(s): Holden DP ; Fickling SA ; Whitley GS ; Nussey SS
Address: Department of Cellular and Molecular Sciences, St George's Hospital Medical School, London, United Kingdom.
Title: **Plasma concentrations of asymmetric dimethylarginine, a natural inhibitor of nitric oxide synthase, in normal pregnancy and preeclampsia.**
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 1998 Mar; 178 (3): 551-6 Journal Code: 3NI
Additional Info: UNITED STATES
Standard No: ISSN: 0002-9378
Language: ENGLISH
Abstract: OBJECTIVE: We investigated the change in the plasma

concentration of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, in early-, mid-, and late-gestation normotensive pregnancies and in gestational age-matched preeclamptic pregnancies and compared the observed changes with changes in blood pressure. STUDY DESIGN: Blood pressure and peripheral plasma asymmetric dimethylarginine concentrations were measured in 20 nonpregnant and 145 pregnant women (33 first-trimester, 50 second-trimester, and 44 third-trimester normotensive pregnancies and 18 third-trimester pregnancies complicated by preeclampsia). In 23 normotensive pregnancies serial plasma asymmetric dimethylarginine concentrations were measured. Statistical analysis was by analysis of variance and linear regression. RESULTS: The blood pressures recorded throughout normal pregnancy were significantly lower than in nonpregnant subjects ($p < 0.0001$). The mean systolic, diastolic, and average blood pressures were significantly higher in the second-trimester groups than in the first-trimester groups, whereas in the third trimester average and diastolic blood pressures were significantly higher than in the second trimester. The mean (+/-SD) systolic and diastolic blood pressures in third-trimester preeclamptic patients was 157.7 +/- 11.2 and 110.9 +/- 8.5 mm Hg. The mean plasma asymmetric dimethylarginine concentration in nonpregnant women was 0.82 +/- 0.31 micromol/L (significantly higher than in normotensive pregnancy, $p < 0.0001$). The plasma asymmetric dimethylarginine concentration was also significantly higher in second-trimester than in first-trimester normotensive groups (respectively, 0.52 +/- 0.20 micromol/L and 0.40 +/- 0.15 micromol/L, $p = 0.001$) and was higher in third-trimester normotensive pregnancy 0.56 +/- 0.23 micromol/L than it was in the second trimester. The asymmetric dimethylarginine concentration in third-trimester preeclamptic patients was 1.17 +/- 0.42 micromol/L ($p < 0.0001$ vs normotensive third-trimester subjects). CONCLUSIONS: It is well recognized that blood pressure falls in early normal pregnancy and rises again toward term. These studies show that the early fall in blood pressure is accompanied by a significant fall in the plasma asymmetric dimethylarginine concentration. Later in pregnancy circulating concentrations increase and, when pregnancy is complicated by preeclampsia, concentrations are higher than in the nonpregnant state. Our data support a role for both asymmetric dimethylarginine and nitric oxide in the changes in

blood pressure seen in both normal and preeclamptic pregnancy.

Author(s): Boccardo P ; Soregaroli M ; Aiello S ; Noris M ; Donadelli R ; Lojacono A ; Benigni A
Address: Mario Negri Institute for Pharmacological Research, Bergamo, Italy.
Title: **Systemic and fetal-maternal nitric oxide synthesis in normal pregnancy and pre-eclampsia.**
Source: Br J Obstet Gynaecol (BRITISH JOURNAL OF OBSTETRICS AND GYNAECOLOGY) 1996 Sep; 103 (9): 879-86
Abstract: OBJECTIVE: To investigate systemic and fetal-placental nitric oxide synthesis by biochemical and molecular biology means in normal human pregnancy and pre-eclampsia. DESIGN AND PARTICIPANTS: Three groups of women were studied: healthy pregnant women (n = 8), pregnant women with pre-eclampsia (n = 8), and age-matched nonpregnant controls (n = 8). Pre-eclamptic patients were treated with nifedipine (30-60 mg/day) for severe hypertension. Systemic nitric oxide synthesis was assessed in normal pregnant women at weeks 18-21, 29-32 and 38-39 and in pre-eclamptic women on admission to the hospital (29-32 weeks, 30 on average), before the morning nifedipine administration. Nonpregnant women were studied twice at four-week intervals as controls. The pattern of nitric oxide biosynthesis in fetal-placental circulation was studied in normal and pre-eclamptic women at the delivery. SETTING: Mario Negri Institute for Pharmacological Research, Bergamo, and the Division of Obstetrics and Gynaecology of the University of Brescia. MAIN OUTCOME MEASURES: Plasma cGMP levels and platelet nitric oxide synthesis, assessed by measuring the conversion of [3H]L-arginine to [3H]L-citrulline as well as intracellular cGMP, were evaluated. Constitutive nitric oxide synthase (EC-NOS) gene expression by Northern blot analysis and nitric oxide release by the conversion of [3H]L-arginine to [3H]L-citrulline were assessed in umbilical vein endothelial cells (HUVEC) and in placenta. Inducible nitric oxide synthase activity was also evaluated in HUVEC exposed to tumour necrosis factor alpha (TNF alpha) and in placenta homogenates incubated in calcium free medium. RESULTS: Plasma cGMP was higher in both normal pregnant and pre-eclamptic women than in nonpregnant controls. In normal pregnancy cGMP rose as early as 18-21 weeks and remained elevated throughout pregnancy. [3H]L-citrulline production and intracellular cGMP were comparable in platelets from all women. EC-NOS gene expression and nitric

oxide synthesis were identical in HUVEC and placenta from normal pregnant and pre-eclamptic women. CONCLUSIONS: Systemic levels of CGMP, the nitric oxide second messenger, are increased in normal pregnancy. Excessive nitric oxide production does not derive from platelets. Pre-eclampsia is not associated with changes in fetal-placental nitric oxide synthesis.

Author(s): Ulm MR ; Plsckinger B ; Pirich C ; Gryglewski RJ ; Sinzinger HF
Address: Department of Obstetrics and Gynecology, University of Vienna, Austria.
Title: **Umbilical arteries of babies born to cigarette smokers generate less prostacyclin and contain less arginine and citrulline compared with those of babies born to control subjects.**
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 1995 May; 172 (5): 1485-7
Abstract: OBJECTIVE: The hypothesis of this study was that umbilical arteries of babies born to smoking mothers produce less nitric oxide and prostacyclin than do those of nonsmoking mothers. STUDY DESIGN: L-Arginine, L-citrulline, L-cysteine, and prostacyclin were measured in the umbilical arteries of 11 babies born to smoking mothers and 16 infants born to nonsmoking controls. The concentrations in the two groups were compared with the modified t test. RESULTS: The generation of prostacyclin was reduced in the umbilical arteries of infants of smoking mothers. Similarly, L-arginine and L-citrulline, but not L-cysteine levels, in these arteries were suppressed compared with those of the nonsmoking controls. CONCLUSION: Along with the known direct vasoconstrictive effect of nicotine, nitric oxide and prostacyclin deficiency may affect the uteroplacental blood flow and contribute to the impaired fetal nutrition and increased perinatal mortality of babies born to women who smoke.

Author(s): Buhimschi I ; Yallampalli C ; Dong YL ; Garfield RE
Address: Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, USA.
Title: **Involvement of a nitric oxide-cyclic guanosine monophosphate pathway in control of human uterine contractility during pregnancy.**
Source: Am J Obstet Gynecol (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY) 1995 May; 172 (5): 1577-84
Abstract: OBJECTIVES: The aims of the study were to investigate whether a nitric oxide-cyclic guanosine monophosphate relaxation pathway is present in the human uterus and whether it differentially inhibits

contractility during pregnancy and labor. STUDY DESIGN: Myometrial strips were obtained from pregnant women who were either in labor or not in labor and from nonpregnant women. Nitrites and cyclic guanosine monophosphate production by the tissues and contractile responses to nitric oxide modifiers were measured. RESULTS: Biochemical assays revealed that nitric oxide (nitrites) and cyclic guanosine monophosphate are generated by the human uterus. Cyclic guanosine monophosphate production by the uterus was increased by L-arginine (the substrate for nitric oxide) and diethylamine/nitric oxide (a nitric oxide donor) and decreased by nitro-L-arginine methyl ester (an inhibitor of nitric oxide synthase). Spontaneous contractility in vitro was increased by nitro-L-arginine methyl ester and decreased by diethylamine/nitric oxide, which furthermore produced a dose-dependent inhibition of contractility, and the median effective dose of inhibition in tissues from nonlaboring pregnant patients (1.5 +/- 0.4 mumol/L) is substantially lower than in tissues from laboring pregnant (21.7 +/- 7.4 mumol/L or nonpregnant (20.8 +/- 4.4 mumol/L) women. These studies show that the nitric oxide-cyclic guanosine monophosphate system exists in the human uterus and that it inhibits contractility. Furthermore, the relaxation responsiveness to nitric oxide is elevated during pregnancy and decreased during labor. CONCLUSION: A nitric oxide-cyclic guanosine monophosphate relaxation pathway is present in the human uterus and may be responsible for maintaining uterine quiescence during pregnancy. A decrease in uterine relaxation responsiveness to nitric oxide at term may play a role in the initiation of labor.

Author(s): Jain KM ; Rush BF Jr ; Seelig RF ; Cheung NK ; Dikdan G

Title: **Changes in plasma amino acid profiles following abdominal operations.**

Source: Surg Gynecol Obstet (SURGERY, GYNECOLOGY AND OBSTETRICS) 1981 Mar; 152 (3): 302-6 Journal Code: VBD

Additional Info: UNITED STATES

Standard No: ISSN: 0039-6087

Language: ENGLISH

Abstract: Plasma amino acid profiles along with hemoglobin, hematocrit, albumin, protein, blood urea nitrogen and serum creatinine values for ten patients undergoing abdominal operations were studied before operation and for 16 days there-after at different intervals. Six patients in the control group were

studied in a similar manner. From the observations obtained, we concluded that total amino acid valued are a more sensitive reflection of patient nutrition in both the preoperative and postoperative periods. In future, total amino acid levels may become part of the nutritional assessment of a patient undergoing an operation. The histidine levels in plasma remain low for the longest period of time, an indication of a great need for histidine. Hence, greater attention should be paid to the histidine content of a diet or solution administered parenterally, or both. In addition, branched chain amino acids, alanine, glycine, cystine, arginine, lysine, tryptophan and threonine are required in greater quantity than the other amino acids as a result of the increased catabolism and partial starvation of the patients postoperatively. In formulation hyperalimentation solutions, an increased need for these amino acids should be kept in mind.

Author(s): Prieto JC ; Serrano-Rios M
Title: **hCS regulation during pregnancy.**
Source: Obstet Gynecol (OBSTETRICS AND GYNECOLOGY) 1976 Sep; 48 (3): 297-301
Abstract: In order to define the homeostatic mechanisms which affect the secretion of human chorionic somatomammotropin (hCS), we have determinated its plasma levels by a radioimmunoassay method in normal, prediabetic, and chemically diabetic pregnant women in basal conditions and after stimuli. Oral glucose failed to modify hCS plasma levels as also did continuous intravenous glucose infusion. Rapid acute intravenous glucose decreased them, suggesting that only sudden changes in maternal plasma glucose can exert a regulatory effect on hCS secretion. Intravenous arginine increased hCS levels, new evidence of the great similarity of structure and function between growth hormone and hCS.

NEPHROLOGY

Author(s): Doi SQ ; Jacot TA ; Sellitti DF ; Hirszel P ; Hirata MH ; Striker GE ; Striker LJ
Address: Department of Medicine, Division of Nephrology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814-4799, USA. sdoi@usuhs.mil
Title: **Growth hormone increases inducible nitric oxide synthase expression in mesangial cells.**
Source: J Am Soc Nephrol (JOURNAL OF THE AMERICAN SOCIETY

OF NEPHROLOGY) 2000 Aug; 11 (8): 1419-25
Abstract: Mice transgenic for bovine growth hormone (GH) develop progressive glomerulosclerosis. However, the proximal signaling events that lead to increased matrix deposition in this pathologic condition are still unclear. Components of the L-arginine metabolic pathway, especially inducible nitric oxide (NO) synthase (iNOS), ornithine aminotransferase (OAT), and ornithine decarboxylase (ODC), have been associated with glomerular scarring. In this study, mesangial cells were treated with GH, and the expression of iNOS, ODC, and OAT was determined using reverse transcription-PCR. In addition, nitrite accumulation in the conditioned media of mesangial cell cultures was measured in the presence or absence of GH. The findings revealed that GH increased iNOS transcript levels in a dose-dependent manner, with the highest levels being attained at GH concentrations of 20 to 50 ng/ml. The GH-induced increase in iNOS transcript levels was accompanied by a significant increase in nitrite concentrations in conditioned media, which was blocked by the addition of L-N(G)-monomethylarginine. The effect of GH (50 ng/ml) in eliciting nitrite production was as potent as that of bacterial lipopolysaccharide (10 &mgr;g/ml). The expression of OAT and ODC, in contrast, was not altered at any of the GH concentrations tested. GH receptor mRNA was also expressed by mesangial cells, independently of the GH concentration present in the cell culture medium. These data indicate that GH may interact with its receptor to regulate the L-arginine/NO pathway in mesangial cells, by directly modulating iNOS expression and NO production, without altering the arginase/OAT/ODC pathway.

Author(s): Dijkhorst-Oei LT ; Boer P ; Rabelink TJ ; Koomans HA
Address: Department of Nephrology and Hypertension, University Hospital Utrecht, The Netherlands.
Title: **Nitric oxide synthesis inhibition does not impair water immersion-induced renal vasodilation in humans.**
Source: J Am Soc Nephrol (JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY) 2000 Jul; 11 (7): 1293-302 Journal Code: A6H
Additional Info: UNITED STATES
Standard No: ISSN: 1046-6673
Language: ENGLISH
Abstract: Nitric oxide (NO) is tonically released in the kidney to maintain renal perfusion and adequate sodium and water clearance. Little is known about

the role of NO in the renal adaptation to an acute volume challenge. This is important for our understanding of pathophysiologic conditions associated with impaired NO activity. This study examined the effects of NO synthesis inhibition on neurohumoral, renal hemodynamic, and excretory responses to head-out immersion (HOI). Seven healthy men underwent four 7-h clearance studies. One study served as a time control study (placebo infusion), and in one study N(G)-monomethyl-L-arginine (L-NMMA; 3 mg/kg priming dose + 3 mg/kg per h) was infused during hours 2 to 5. In a third and fourth clearance study, HOI was applied from hours 3 to 5, during infusion of either placebo or L-NMMA. To assess the degree of NO synthesis inhibition, the effect of L-NMMA on [(15)N]-arginine-to-[(15)N]-citrulline conversion rate was studied in four others. HOI decreased mean arterial pressure (MAP) from 87 +/- 3 to 76 +/- 2 mmHg and renal vascular resistance (RVR) from 82 +/- 6 to 70 +/- 7 mmHg. min/L, and increased sodium excretion (UNaV) from 110 +/- 27 to 195 +/- 29 micromol/min and flow (UV) from 14.4 +/- 1.4 to 15.8 +/- 1.4 ml/min. L-NMMA caused profound and sustained increases in MAP and RVR and decreases in UNaV and UV. HOI superimposed on L-NMMA infusion decreased the elevated MAP from 93 +/- 4 to 83 +/- 2 mmHg and RVR from 111 +/- 9 to 95 +/- 7 mmHg. min/L, and increased UNaV from 41 +/- 8 to 95 +/- 15 micromol/min and UV from 10.0 +/- 1.1 to 12.7 +/- 1.4 ml/min. The relative changes were not significantly different from the effects of HOI without L-NMMA infusion. HOI decreased plasma renin activity and aldosterone and increased plasma atrial natriuretic peptide and urinary cGMP. L-NMMA decreased urinary cGMP, but did not affect the plasma hormones or the changes induced by HOI. L-NMMA decreased the [(15)N]-arginine-to-[(15)N]-citrulline conversion rate to one-third of baseline. The results indicate that in a state of NO deficiency in humans, the kidney can still respond to an acute volume challenge with vasorelaxation, diuresis, and natriuresis.

Author(s): Langen H ; von Kietzell D ; Byrd D ; Arslan-Kirchner M ; Vester U ; Stuhrmann M ; Dsrk T ; Saar K ; Reis A ; Schmidtke J ; Brodehl J
Address: Department of Pediatric Nephrology and Metabolic Disorders, Medical School Hannover, Germany. Hendrik.Langen@t-online.de
Title: **Renal polyamine excretion, tubular amino acid reabsorption and molecular genetics in cystinuria.**

Source: Pediatr Nephrol (PEDIATRIC NEPHROLOGY) 2000 May; 14 (5): 376-84

Abstract: Cystinuria is an autosomal recessive disorder of the tubular and intestinal resorption of cystine, ornithine. lysine and arginine leading to nephrolithiasis. Three cystinuria types can be distinguished by the mode of inheritance (true recessive or intermediate) and by the pattern of the intestinal amino acid transport. In the present study phenotypes were assessed by the urinary excretion of amino acids related to creatinine, the percentage tubular amino acid reabsorption and the urinary excretion of polyamines as a possible indicator of the intestinal transport defect. However, our thorough phenotyping did not reveal more than two cystinuria types. Genotypes were examined in linkage analyses and single-strand conformation polymorphism-based mutation identification. The SLC3A1 mutations M467T and T216M were disease causing in our homozygous patients of type I cystinuria. We can show the association of type I cystinuria with SLC3A1 and of non-type I cystinuria with a yet unidentified gene on chromosome 19q13.1. Our phenotype and genotype analyses provide evidence for only two types of cystinuria in the investigated patient cohort.

Author(s): Combet S ; Miyata T ; Moulin P ; Pouthier D ; Goffin E ; Devuyst O
Address: Division of Nephrology, Universit* Catholique de Louvain Medical School, Brussels, Belgium.

Title: **Vascular proliferation and enhanced expression of endothelial nitric oxide synthase in human peritoneum exposed to long-term peritoneal dialysis.**

Source: J Am Soc Nephrol (JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY) 2000 Apr; 11 (4): 717-28

Abstract: Long-term peritoneal dialysis (PD) is associated with alterations in peritoneal permeability and loss of ultrafiltration. These changes originate from increased peritoneal surface area, but the morphologic and molecular mechanisms involved remain unknown. The hypothesis that modifications of activity and/or expression of nitric oxide synthase (NOS) isozymes might play a role in these modifications, via enhanced local production of nitric oxide, was tested in this study. NOS activities were measured by the L-citrulline assay in peritoneal biopsies from seven control subjects, eight uremic patients immediately before the onset of PD, and 13 uremic patients on short-term (<18 mo, n = 6) or long-term(>18 mo, n = 7) PD.

Peritoneal NOS activity is increased fivefold in long-term PD patients compared with control subjects. In uremic patients, NOS activity is positively correlated with the duration of PD. Increased NOS activity is mediated solely by Ca(2+)-dependent NOS and, as shown by immunoblotting, an upregulation of endothelial NOS. The biologic relevance of increased NOS in long-term PD was demonstrated by enhanced nitrotyrosine immunoreactivity and a significant increase in vascular density and endothelial area in the peritoneum. Immunoblotting and immunostaining studies demonstrated an upregulation of vascular endothelial growth factor (VEGF) mostly along the endothelium lining peritoneal blood vessels in long-term PD patients. In the latter, VEGF colocalized with the advanced glycation end product pentosidine deposits. These data provide a morphologic (angiogenesis and increased endothelial area) and molecular (enhanced NOS activity and endothelial NOS upregulation) basis for explaining the permeability changes observed in long-term PD. They also support the implication of local advanced glycation end product deposits and liberation of VEGF in that process.

Author(s): Arai J ; Kubota K ; Hara Y ; Tsuchiya K ; Naruse K ; Naruse M ; Nihei H ; Sugino N
Address: Fourth Department of Internal Medicine, Tokyo Women's Medical College, Japan.
Title: [Natriuresis and blood pressure in patients with chronic renal failure following L-arginine infusion]
Source: Nippon Jinzo Gakkai Shi (NIPPON JINZO GAKKAI SHI. JAPANESE JOURNAL OF NEPHROLOGY) 2000 Jan; 42 (1): 11-5 Journal Code: KMK
Additional Info: JAPAN
Standard No: ISSN: 0385-2385
Language: JAPANESE
Abstract: Nitric oxide (NO) is known to be generated from L-arginine and may regulate glomerular filtration, tubular sodium reabsorption, and renin secretion. Impairment of renal function might influence NO production secondary to endothelial dysfunction, decreased NO synthesis and increased activity of arginine analogues inhibiting NO synthase. In this study, we evaluated the effect of L-arginine on the blood pressure and urinary sodium excretion in patients with chronic renal failure. A 300-ml dose of 10% L-arginine solution was administered intravenously over 30 min and blood pressure was monitored every 10 min under basal conditions and for 120 min after infusion. The patients were

divided into two groups based on the reduction in mean blood pressure (dMBP) following infusion, namely non-responders (dMBP < 10 mmHg) and responders (dMBP > 10 mmHg). Urine and blood samples were collected to determine electrolytes, urinary NO2 + NO3 by the Griess method, urinary cGMP, plasma renin activity (PRA), and the plasma aldosterone concentration (PAC). L-arginine significantly decreased MBP in 8 patients and caused no significant change in 10 patients. Urinary sodium excretion and the NO2 + NO3 level were significantly increased following L-arginine infusion and the increment of fractional excretion of sodium was higher in responders. However, there were no significant changes in PRA, PAC, and cGMP. Our findings suggest that a vasodilator effect of NO induced by L-arginine loading may, at least in part, be associated with increased renal sodium excretion in patients with chronic renal failure.

Author(s): Lee J ; Kim SW ; Kook H ; Kang DG ; Kim NH ; Choi KC
Address: Departments of Physiology, Internal Medicine and Pharmacology, Chonnam University Medical School, Kwangju, Korea.
Title: **Effects of L-arginine on cyclosporin-induced alterations of vascular NO/cGMP generation.**
Source: Nephrol Dial Transplant (NEPHROLOGY, DIALYSIS, TRANSPLANTATION) 1999 Nov; 14 (11): 2634-8
Abstract: BACKGROUND: Cyclosporin (CsA)-induced vascular dysfunction has been attributed to a diminished role of the nitric oxide (NO)/cGMP-mediated vasodilator mechanism. The present study was aimed at investigating whether L-arginine, the substrate of NO synthesis, ameliorates CsA-induced vascular dysfunction. METHODS: Male Sprague-Dawley rats were used throughout the study. The thoracic aorta was isolated from normal rats and acutely treated with CsA (10(-4) mol/l, 60 min) in vitro, or the aorta was taken from rats treated with CsA (25 mg/kg/day, i.m., 1 week). The vascular relaxation response to acetylcholine, and tissue levels of NO metabolites and cGMP were determined. The vascular expression of NO synthase (NOS) isoforms was also determined by western blot analysis. RESULTS: Acute treatment with CsA in vitro markedly attenuated the vasorelaxation response to acetylcholine, which was completely restored by L-arginine. The vascular accumulation of NO metabolites in response to acetylcholine was decreased significantly by CsA, which was prevented by cotreatment with L-arginine. CsA decreased the cGMP accumulation in response to both acetylcholine and sodium nitroprusside. L-Arginine restored, although not completely,

acetylcholine-stimulated cGMP generation, whereas it did not affect sodium nitroprusside-stimulated cGMP generation. Following chronic CsA treatment in the whole animal, the vasorelaxation response to acetylcholine was decreased significantly along with tissue levels of NO metabolites; this was preserved by L-arginine-supplementation. Vascular expression of iNOS protein was decreased by CsA treatment along with decreased tissue accumulation of NO metabolites. L-Arginine supplementation did not modify the altered expression of NOS proteins. CONCLUSION: These results suggest that CsA causes an L-arginine-sensitive vascular dysfunction which is associated with impaired generation of NO and cGMP.

Author(s): Rump LC ; Vonend O ; Oberhauser V
Address: Medizinische UniversitStsklink Freiburg, Germany.
Title: ATP release and degradation in the kidney: modulatory role of neuropeptide Y (NPY).
Source: Nephrol Dial Transplant (NEPHROLOGY, DIALYSIS, TRANSPLANTATION) 1999; 14 Suppl 4: 48-9
Descriptor: Adenosine Triphosphate -- Metabolism
Kidney -- Metabolism
Neuropeptide Y -- Physiology
Arginine -- Analogs & Derivatives
Rats
Animal
Support, Non-U.S. Gov't
Chemical Subst: 0 (BIBP 3226)
0 (Neuropeptide Y)
56-65-5 (Adenosine Triphosphate)
7004-12-8 (Arginine)

Author(s): Zhang XZ ; Ghio L ; Ardissino G ; Tirelli AS ; Dacco V ; Testa S ; Claris-Appiani A
Address: Clinica Pediatrica II, Universita di Milano, Milan, Italy.
Title: **Renal and metabolic effects of L-arginine infusion in kidney transplant recipients.**
Source: Clin Nephrol (CLINICAL NEPHROLOGY) 1999 Jul; 52 (1): 37-43 Journal Code: DEY
Additional Info: GERMANY
Standard No: ISSN: 0301-0430
Language: ENGLISH
Abstract: AIM AND METHODS: In order to investigate the role of kidney damage on renal response to L-arginine (L-Arg) infusion in transplant patients receiving cyclosporine A (CsA) treatment, we assessed systemic and glomerular hemodynamic variables, the fraction excretion of urinary sodium, albumin, cyclic GMP (as an index of nitric oxide (NO)

production from L-Arg) and urea excretion (as an index of ureagenesis), and glucoregulatory hormone levels in five normal volunteers and 21 renal allograft recipients (aged 10-20 years) treated with CsA, 10 with normal renal function and 11 with chronic renal insufficiency. RESULTS: In the normal subjects, L-Arg infusion (290 mg/min/1.73 m2 for 1 h) significantly reduced mean arterial pressure (MAP) (76+/-7 to 70+/-5 mmHg) and renal vascular resistance (RVR), and increased GFR (103+/-9 to 122+/-7 min/1.73 m2), RPF, urinary cyclic GMP excretion (0.40+/-0.1 to 0.60+/-0.1 nmol/100 ml glomerular filtrate (GF)), and sodium and albumin excretion. Neither the patients with chronic graft dysfunction nor those with a normal graft responded to L-Arg infusion: RVR remained high, and MAP, GFR, RPF, fractional excretion of sodium and urinary excretion of albumin and cyclic GMP were unchanged in both groups of patients. Glucagon, insulin and urinary urea excretion rose significantly in controls and both patient groups. CONCLUSION: The hemodynamic effects of L-Arg infusion were inhibited in the patients, regardless of their degree of renal function, possibly because L-Arg-NO production was blunted.

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Title: **From rats to man: a perspective on dietary L-arginine supplementation in human renal disease.**
Source: Nephrol Dial Transplant (NEPHROLOGY, DIALYSIS, TRANSPLANTATION) 1999 Jul; 14 (7): 1640-50 Journal Code: N7J
Additional Info: ENGLAND
Standard No: ISSN: 0931-0509
Language: ENGLISH
Abstract: Experimental studies have shown both therapeutic and detrimental consequences of modifying dietary L-arginine intake in renal diseases which likely reflect the complexity of L-arginine metabolism. L-Arginine intake is semi-essential and provides substrate for a number of L-arginine metabolites involved in renal pathology. Dietary L-arginine restriction has been identified as a key mediator of the beneficial effects of low protein diets on human renal fibrosis. Supplementing dietary L-arginine in renal diseases with increased iNOS expression appears to be detrimental and thus, may be harmful in immune-mediated human kidney disorders. Increasing L-arginine intake is beneficial in experimental models of hypertensive

renal disease. Based upon available data, we believe additional questions must be answered experimentally, not only to prevent an adverse outcome in humans, but to enhance our chances of human trials which will result in substantially better amelioration of disease than currently available.

Author(s): Jerkic M ; Varagic J ; Jovovic D ; Radujkovic-Kuburovic G ; Nastic-Miric D ; Adanja-Grujic G ; Markovic-Lipkovski J ; Dimitrijevic J ; Miloradovic Z ; Vojvodic SB
Address: Institute for Medical Research, Medical School, Belgrade, Yugoslavia.
Title: L-arginine reduces tubular cell injury in acute post-ischaemic renal failure.
Source: Nephrol Dial Transplant (NEPHROLOGY, DIALYSIS, TRANSPLANTATION) 1999 Jun; 14 (6): 1398-407
Abstract: BACKGROUND: The pathophysiology of renal ischaemia, resulting in tubular cell injury and leading to acute renal failure (ARF), remains unclear. An ever-increasing number of investigations focus on a possible role of nitric oxide (NO) in regulating circulation during ARF. In this context, we investigated the influence of chronic stimulation or inhibition of NO synthesis, or both, on haemodynamic parameters, histology and plasma renin activity (PRA) after ischaemia-reperfusion injury of rat kidneys. METHODS: Experiments were performed on adult, male Wistar rats. Before induction of ARF, a group of animals was treated with a NO synthesis inhibitor (L-NAME) and another group was treated with a precursor of NO synthesis (L-arginine). The animals received those substances for 4 weeks. Control groups received the same amount of tap water for 4 or 8 weeks and were divided into groups with ARF (4 weeks--ARF group and 8 weeks ARF group) and a sham-operated group. Another group of rats was treated first with L-NAME and then with L-arginine in their drinking water, for 4 weeks for each of these two substances. All parameters were evaluated 24 h after the induction of ischaemic ARF or the sham operation. RESULTS: Our results show that such long-term stimulation of NO release by L-arginine improved renal haemodynamics in the ischaemic form of ARF. Renal blood flow (RBF) increased by 96% in the L-arginine-treated rats with ARF compared with the group with ARF alone. Inhibition of NO synthesis worsens renal haemodynamics after ARF. However, this aggravation can be reversed by L-arginine. The rate of water reabsorption was reduced in all groups with ARF, but this reduction was least in

the group treated with L-arginine. The rate of Na+ reabsorption was reduced in all groups 24 h after renal ischaemia, but a significant decrease was observed after the inhibition of NO synthesis. Histological examination of the kidney specimens showed that morphological changes were least in the rats treated with L-arginine, when compared with all other groups with ARF. Nevertheless, the lesions were most prominent in the L-NAME+ARF group. In this group, the areas of corticomedullar necrosis were more widespread in comparison with other groups, especially the L-arginine group where only swelling of the proximal tubular cells was observed. Treatment with L-NAME was not accompanied by any significant alteration in the plasma concentration of angiotensin I (ANG I), while in the group treated with L-arginine ANG I had a tendency to decrease. CONCLUSIONS: Acute post-ischaemic renal failure may be alleviated by administering the NO substrate (L-arginine). NO acts cytoprotectively on tubular epithelial cells in ischaemia--reperfusion injury of rat kidney. Evidence of this comes from both histopathological findings and increased tubular water and sodium reabsorption. However, inhibition of NO synthesis (provoked by L-NAME) worsens renal haemodynamics and aggravates morphological changes after ARF. These aggravations can, however, be reversed by L-arginine.

Database: MEDLINE
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* Libraries that Own Item: 128
Author(s): Tom* LA ; Yu L ; de Castro I ; Campos SB ; Seguro AC
Address: Department of Nephrology, University of S‹o Paulo School of Medicine, Brazil.
Title: **Beneficial and harmful effects of L-arginine on renal ischaemia**.
Source: Nephrol Dial Transplant (NEPHROLOGY, DIALYSIS, TRANSPLANTATION) 1999 May; 14 (5): 1139-45
Abstract: BACKGROUND: The role of nitric oxide (NO) in acute renal failure (ARF) is not yet completely understood. L-Arginine (L-arg) is protective against different ARF models, while L-arg addition in isolated proximal tubules enhances hypoxia/reoxygenation (H/R) injury. The aim of this study was to evaluate the effects of L-arg on renal ischaemia. METHODS: In in vivo studies, Wistar rats were subjected to 60 min renal artery clamping, and renal function was evaluated 2 and 15 days after ischaemia. Four groups were studied: (1) control; (2) acute L-arg (50 mg/kg/bw i.v.); (3) L-nitro-arginine-methyl esther (L-NAME; 0.5 mg/kg/bw i.v.); and (4) chronic L-arg (L-arg 0.25%

in drinking water/7 days). For the in vitro studies, proximal tubules (PTs), isolated by collagenase digestion and Percoll gradient, were studied from three groups: (1) untreated; (2) L-arg-treated (L-arg 0.25% in drinking water/7 days); and (3) L-NAME-treated rats (3 mg/kg in drinking water/7 days). PTs were kept oxygenated or subjected to 15 min hypoxia (H-15) and 35 min reoxygenation (R-35). In some experiments, additional doses of L-arg and L-NAME were administered. Cell injury was assessed by lactate dehydrogenase (LDH) release. NO production was evaluated by NO2-/NO3- measurement (Griess reaction) in both urine and isolation medium. RESULTS: After 2 days, L-arg infusion protected against ischaemia compared with control rats (0.4 vs 0.2 ml/min/100 g, P < 0.001), while neither L-NAME nor chronic L-arg supplementation ameliorated renal function. After 15 days, both acute and chronic L-arg groups showed a higher glomerular filtration rate (0.6 and 0.75 ml/min/100 g) compared with control rats (0.3 ml/min/100 g, P < 0.05) and L-NAME-treated rats (0.2 ml/min/100 g, P < 0.05). Despite similar recovery in both L-arg groups, the mortality rate was 25% in the chronic L-arg group. Tubular function was also better preserved in the acute L-arg group. PTs isolated from L-arg-treated rats were more sensitive to isolation injury. L-Arg addition enhanced H/R injury (44.9 vs 51.8%, P < 0.05), whereas L-NAME addition protected (44.9 vs 24%, P < 0.001) in untreated rats. In L-arg-treated rats, addition of L-arg did not enhance H/R injury (49.6 vs 53.5%, NS) and L-NAME was still protective (49.6 vs 32.3%, P < 0.001). In PTs from L-NAME-treated rats, L-arg addition also did not enhance H/R injury (50 vs 54%, NS) whereas L-NAME was protective (50 vs 27%, P < 0.001). NO2-/NO3- production paralleled L-arg and L-NAME supplementation. CONCLUSION: It was demonstrated that acute L-arg infusion was beneficial in in vivo renal ischaemia while it was harmful in isolated H/R tubules. In contrast, chronic L-arg supplementation was deleterious both in in vivo and in vitro renal ischaemia, suggesting that injurious effects had overcome the beneficial effects during excess NO exposure.

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Address: Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA.
Title: Can L-arginine manipulation reduce renal disease?
Source: Semin Nephrol (SEMINARS IN NEPHROLOGY) 1999 May; 19 (3): 304-9 Journal Code: SER

Additional Info: UNITED STATES
Standard No: ISSN: 0270-9295
Language: ENGLISH
Abstract: The administration of L-arginine to normal animals leads to an increase in renal plasma flow and glomerular filtration rate (GFR). Administration on a chronic basis of N-nitro-L-arginine methylester (L-NAME), an antagonist of L-arginine, increases blood pressure and reduces the ultrafiltration coefficient. In rats with ureteral obstruction, the administration of L-arginine increases GFR and renal blood flow in the postobstructive kidney. Administration of L-arginine decreased the macrophage infiltration of the renal parenchyma that occurs in this model. L-arginine administration also blunted the increases in interstitial volume, collagen deposition, and expression of alpha-smooth muscle actin in the obstructed kidney. L-arginine administration to rats with subtotal nephrectomy reduced proteinuria and the number of abnormal glomeruli. Some of these effects may be mediated by nitric oxide (NO). In rats with diabetes, administration of L-arginine decreased hyperfiltration and proteinuria. The role of arginine and NO in glomerular diseases is controversial. In general most of the evidence indicates a beneficial change in the renal pathology and function in animals with glomerulonephritis receiving L-arginine. Most of the evidence indicates that the L-arginine-NO pathway has an important role in ameliorating hypertension, renal disease, inflammation and atherosclerosis.

ANTI AGING BIOLOGY

Author: Chauhan, A; More, RS; et.al.
Title: **Aging associated enothelial dysfunction in humans is reversed by L-Arginine**.
Source: Circulation (supplement) 92 (1995) I-K.

Author: Hurson, M; Regan, MC; et al
Title: **Metabolic effects of arginine in a healthy elderly population.**.
Source: Journal of Parental and Enteral Nutrition, 19 (1995) 227-230.

Author(s): Walrand S ; Chambon-Savanovitch C ; Felgines C ; Chassagne J ; Raul F ; Normand B ; Farges MC ; Beaufrere B ; Vasson MP ; Cynober L
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Title: Aging: a barrier to renutrition? Nutritional and immunologic evidence in rats.
Source: Am J Clin Nutr (AMERICAN JOURNAL OF CLINICAL NUTRITION) 2000 Sep; 72 (3): 816-24 Journal Code: 3EY
Additional Info: UNITED STATES
Standard No: ISSN: 0002-9165
Language: ENGLISH
Abstract: BACKGROUND: Previous reports suggest that correcting the malnourished state is more difficult in elderly people than in younger ones and that protein requirements may be higher in elderly than in younger adults. OBJECTIVE: The aim of this study was to establish whether malnourished old rats respond to protein-supplemented nutritional repletion as do young adult rats. DESIGN: Adult (3 mo old) and old (22 mo old) rats were submitted to dietary restriction programs that induced similar metabolic and nutritional alterations. Malnourished adult and old rats were then killed (R groups) or refed for 1 wk with a high-protein diet (HPD; 23% protein) or a very-high-protein diet (VHPD; 27% protein). Control groups at both ages were fed ad libitum throughout the experiment. Effects of food repletion were evaluated in terms of protein metabolism, intestinal histomorphometry, and nonspecific immune status. RESULTS: In adult rats, HPD sufficed to increase body weight and restore basal values of liver weight and protein content (P: < 0.01 compared with the R adult group), nitrogen balance (P: < 0.01 compared with the R adult group), and hydrogen peroxide production by polymorphonuclear neutrophils and monocytes (P: < 0.01 compared with the R group); VHPD had no supplementary effect except on nitrogen balance. In old rats, HPD was less effective and greater benefit was observed with VHPD in terms of body weight gain (10%; P: < 0.01 compared with the old group fed HPD), albuminemia, muscle weight and protein content, plasma arginine concentration, and hydrogen peroxide production by stimulated polymorphonuclear neutrophils and monocytes compared with the old R group (P: < 0.01). CONCLUSION: Aging is a significant variable affecting the response to nutritional support.

Author(s): Yu W ; Juang S ; Lee J ; Liu T ; Cheng J
Address: Department of Pharmacology, College of Medicine, National Cheng Kung University, Taiwan 70101, Republic of, Tainan City, China.
Title: **Decrease of neuronal nitric oxide synthase in the cerebellum of aged rats**.
Source: Neurosci Lett (NEUROSCIENCE LETTERS) 2000 Sep 8;

291 (1): 37-40
Abstract: Nitric oxide (NO) is produced as an important neurotransmitter in the central nervous system (CNS) to participate in some pathophysiological pathways. In the present study, change of neuronal nitric oxide synthase (nNOS) was examined in isolated cerebellum of Wistar rats aged from 2 to 24 months. Northern blot showed a lower mRNA level of nNOS in rats aged 6, 12 and 24 months than that in rats aged 2 months. Western blot analysis also indicated that the expression of nNOS protein was lower in rats aged 6, 12 and 24 months than that of 2 months rats. However, the activity of nNOS determined by conversion of [(3)H] L-arginine to [(3)H] L-citrulline was decreased significantly in rats aged 24 months only. These results indicate the decrease of NOS expression in cerebellum of aged rat that seems helpful to explain the causes of malfunction in CNS of aged mammalian.

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Title: Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes.
Source: Circulation (CIRCULATION) 2000 Jun 27; 101 (25): 2896-901
Abstract: BACKGROUND: Aging is associated with increased cardiovascular risk and endothelial dysfunction. Since exercise can improve endothelium-dependent vasodilation, in the present study we tested whether long-term physical activity could prevent aging-related endothelial dysfunction. METHODS AND RESULTS: In 12 young and elderly (age 26.9+/-2.3 and 62.9+/-5.8 years, respectively) healthy sedentary subjects and 11 young and 14 elderly matched athletes (age 27.5+/-1.9 and 66.4+/-6.1 years, respectively), we studied (with strain-gauge plethysmography) forearm blood flow modifications induced by intrabrachial acetylcholine (0.15, 0.45, 1.5, 4.5, and 15 microg/100 mL per minute), an endothelium-dependent vasodilator, at baseline, during infusion of N(G)-monomethyl-L-arginine (L-NMMA) (100 microg/100 mL forearm tissue per minute), a nitric oxide-synthase inhibitor, vitamin C (8 mg/100 mL forearm tissue per minute), an antioxidant, and finally under simultaneous infusion of L-NMMA and vitamin C. The response to sodium nitroprusside (1, 2, and 4 microg/100 mL forearm tissue per minute) was also evaluated. In young athletes and sedentary subgroups,

vasodilation to acetylcholine was inhibited by L-NMMA and was not changed by vitamin C. In elderly subjects, vasodilation to acetylcholine was blunted as compared with young subjects in both control subjects and athletes, whereas the response to sodium nitroprusside was similar. Moreover, in elderly athletes, vitamin C did not change the vasodilation to acetylcholine. In contrast, in elderly sedentary subjects, the response to acetylcholine was resistant to L-NMMA. In this subgroup, vitamin C increased the vasodilation to acetylcholine and restored the inhibiting effect of L-NMMA. CONCLUSIONS: These results suggest that regular physical activity can at least in part prevent the age-induced endothelial dysfunction, probably the restoration of nitric oxide availability consequent to prevention of production of oxidative stress.

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Title: Effect of age and menopause on serum concentrations of pentosidine, an advanced glycation end product.
Source: J Gerontol A Biol Sci Med Sci (JOURNALS OF GERONTOLOGY. SERIES A, BIOLOGICAL SCIENCES AND MEDICAL SCIENCES) 2000 Mar; 55 (3): M137-40 Journal Code: CBA
Additional Info: UNITED STATES
Standard No: ISSN: 1079-5006
Language: ENGLISH
Abstract: BACKGROUND: Pentosidine is an advanced glycation end product. Our aim is to investigate (a) the age-related change of serum pentosidine and (b) the effect of menopause on serum pentosidine. METHODS: Using the high-performance liquid-chromatography method with column switching, we measured serum pentosidine in 140 healthy women aged 20-93 years. Serum creatinine was also measured. The samples of 13 young and 13 old subjects were used for the measurements of free pentosidine and fractions of pentosidine. Free pentosidine was measured without hydrolysis, and the fractions were measured with a 10,000 mol wt cutoff filter. To investigate the effect of menopause on pentosidine, two biochemical markers for bone turnover (CTx and osteocalcin) were measured in age-matched premenopausal and postmenopausal women (16 in each group). RESULTS: Serum pentosidine significantly increased with age ($r = .702$, $p < .0001$). The values of serum pentosidine for the groups beyond the age of 50

were significantly higher than those for the younger groups. The value for the group aged 80-93 years was three times higher than that for the group aged 20-29 years. Serum pentosidine moderately and significantly correlated to serum creatinine (r = .483, p = .0001). Free pentosidine was detected in only 3 of 13 young subjects and 2 of 13 old subjects. The ratio of free to total pentosidine was 2.9% and 1.2% in young and old subjects, respectively. Pentosidine <10,000 mol wt was not detected in all subjects. Pentosidine >10,000 mol wt was detected in all subjects. Serum CTx and osteocalcin significantly increased in postmenopausal women compared with those of pre-menopausal women. There was no significant change in serum pentosidine between the premenopause group and the postmenopause group. CONCLUSION: Serum pentosidine significantly increased with age in healthy subjects aged 20-93 years and correlated to serum creatinine. The changes of fractions of pentosidine with aging were not observed. There was no effect of menopause on pentosidine.

Database: MEDLINE
Ownership: Check the catalogs in your library.
* Libraries that Own Item: 979
Author(s): Colao A ; Cuocolo A ; Di Somma C ; Cerbone G ; Della Morte AM ; Nicolai E ; Lucci R ; Salvatore M ; Lombardi G
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Title: **Impaired cardiac performance in elderly patients with growth hormone deficiency.**
Source: J Clin Endocrinol Metab (JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM) 1999 Nov; 84 (11): 3950-5
Abstract: Several evidences indicate that GH and/or insulin-like growth factor I (IGF-I) are involved in the regulation of cardiovascular function. In patients with childhood and adulthood-onset GH deficiency (GHD), the impairment of cardiac performance is manifest primarily as a reduction in the left ventricular (LV) mass (LVM), inadequacy of LV ejection fraction both at rest and at peak exercise, and abnormalities of LV diastolic filling. No study has been reported to date in elderly GHD patients that investigated cardiac function. In particular, it is unknown whether cardiac function is modified in accordance with

patients' age as a physiological response to aging, as in normal subjects the rate and extent of LV filling are reduced with age. This study was designed to evaluate heart morphology and function, by echocardiography and equilibrium radionuclide angiography, respectively, in rigorously selected elderly patients with GHD but without evidence of other complications able to affect cardiac performance. Eleven patients with hypopituitarism (6 men and 5 women, aged 60-72 yr) and 11 sex- age- and body mass index-matched healthy subjects entered this study. None of the patients and controls presented with or had previously suffered from other concomitant diseases, such as diabetes mellitus, coronary artery diseases, long-standing hypertension, and hyperthyroidism, which could affect cardiac function. All patients had been previously operated on via the transsphenoidal and/or transcranic route for nonfunctioning pituitary adenoma, meningioma, or craniopharyngioma, and 6 of them had been irradiated. Eight patients had FSH/LH insufficiency, 5 had TSH insufficiency, and 6 had ACTH insufficiency, appropriately replaced. All subjects were tested with the combined arginine plus GHRH test showing a GH response below 9 microg/L. No significant difference was found in plasma IGF-I levels (49.2 +/- 8.5 vs. 71.8 +/- 7.5 microg/L) between patients and controls. However, IGF-I levels were lower than the normal range in 8 patients and 3 controls. Interventricular septum thickness (9.1 +/- 0.2 vs. 9.1 +/- 0.2 mm), LV posterior wall thickness (9.1 +/- 0.2 vs. 9.0 +/- 0.2 mm), and LVM after correction for body surface area (97.6 +/- 1.8 vs. 99.9 +/- 1.5 g/m2) were similar in patients and controls. Similarly, the LV ejection fraction at rest was similar in patients and controls (57.1 +/- 2% vs. 63.2 +/- 2.5%; P = NS), and it was normal (> or = 50%) in all controls and in 10 of 11 patients. By contrast, the LV ejection fraction at peak exercise was markedly depressed in elderly GHD patients compared to age-matched controls (51 +/- 2.5% vs. 73.3 +/- 3%; P < 0.001). A normal response (> or = 5% increase compared to basal value) of LV ejection fraction at peak exercise was found in 8 controls (72.7%) and in 2 of 11 patients (18.2%). No difference was found in the peak rate of LV filling, whether peak filling rate was normalized to end-diastolic volume (2.5 +/- 0.2 vs. 2.6 +/- 0.2 end-diastolic volume/s) or stroke volume (4.3 +/- 0.3 vs. 4.0 +/- 0.3 stroke volume/s), between patients and controls. Finally, exercise duration was

significantly shorter in elderly GHD patients than in age-matched controls (7.2 +/- 2.1 vs. 9.1 +/- 0.2 min; P < 0.01). In the patient group, the GH peak after arginine plus GHRH test was significantly correlated with the LV ejection fraction at rest (r = 0.822; P < 0.01), whereas IGF-I was significantly correlated with the peak rate of LV filling whether the peak filling rate was normalized to end-diastolic volume (r = -0.863; P < 0.001) or stroke volume (r = -0.616; P < 0.05) or expressed as the ratio of peak filling rate to peak ejection fraction rate (r = -0.736; P < 0.01). Disease duration was significantly correlated with heart rate at peak exercise (r = 0.614; P < 0.05) and with systolic and diastolic blood pressures both at rest (r = 0.745; P < 0.01 and r = 0.650; P < 0.05) and at peak exercise (r = 0.684; P < 0.05 and r =

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Title: **Characterization and regional distribution of nitric oxide synthase in the human brain during normal ageing.**
Source: Brain Res (BRAIN RESEARCH) 1999 Jul 10; 834 (1-2): 128-35 Journal Code: B5L
Additional Info: NETHERLANDS
Standard No: ISSN: 0006-8993
Language: ENGLISH
Abstract: Nitric oxide (NO) is a highly diffusible cellular mediator generated from L-arginine by the enzyme nitric oxide synthase (NOS). As little is known about the regional distribution of NOS in the human brain, we examined the distribution pattern of nitric oxide synthase activity in 28 regions of the human brain using the [(3)H]L-citrulline formation assay. To elucidate which isoforms contribute to the total NOS activity we performed Western blot analysis of neuronal, inducible and endothelial NOS. We further determined brain levels of arginine and citrulline as a potential index of NOS activity pre mortem. NOS activity appears to remain unaltered during ageing and is independent of post mortem delay, gender or sample storage time. We identified a regional pattern of NOS distribution with highest levels of NOS activity in the substantia innominata, cerebellar cortex, nucleus accumbens and subthalamicus, whereas lowest levels were measured in the corpus callosum, thalamus, occipital cortex, and dentate nucleus. nNOS was

measured throughout the brain, in contrast iNOS and eNOS were not detectable. We therefore conclude that primarily nNOS is responsible for NOS activity in the human brain. Levels of citrulline were higher than those of arginine, but did not correlate with the enzyme activity, suggesting that these parameters are unsuitable for testing NOS activity premortem. The characterization and topographical pattern of NOS in the human brain during normal ageing may assist our understanding of the physiological role of NO and its relevance in Parkinson's and Alzheimer's disease, alcoholism, schizophrenia and AIDS. Copyright 1999 Elsevier Science B.V.

ENDOCRINOLOGY

Author: Cooke, JP; Singer, AH; et al.
Title: **Learning by diffusion: Nitric oxide may spread memories**.
Source: Nature, 263 (1994) 466.

Author: Copknschi, G; Wegienka, LC; et al.l
Title: **Effect of arginine on serum levels of insulin and growth hormone in obsese subjects**.
Source: Metabolism, 16(1967) 485-491.

Author(s): Moorkens G ; Berwaerts J ; Wynants H ; Abs R
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Title: **Characterization of pituitary function with emphasis on GH secretion in the chronic fatigue syndrome.**
Source: Clin Endocrinol (Oxf) (CLINICAL ENDOCRINOLOGY) 2000 Jul; 53 (1): 99-106
Abstract: OBJECTIVE: Previous studies have revealed that hormonal disturbances may accompany the chronic fatigue syndrome (CFS). Changes in the secretion of the pituitary-adrenal axis have been demonstrated, as well as abnormalities in the GH-IGF-I axis. However, data have not always been well characterized and were sometimes conflicting. The small number of CFS patients investigated in earlier studies may have played a role in the interpretation of the results. SUBJECTS AND DESIGN: Hormonal testing was performed in 73 nonobese CFS patients and nonobese 21 age-and gender-matched healthy controls. We investigated GH, ACTH and cortisol responses to insulin-induced hypoglycaemia. In a subgroup of patients arginine and clonidine stimulation for GH was also

performed. Nocturnal secretion of GH, ACTH and cortisol were determined. Serum levels of IGF-I, prolactin, TSH, and free thyroxine were also measured. Visceral fat mass was assessed by CT scanning. RESULTS: GH response to insulin induced hypoglycaemia assessed by peak value (17.0 +/- 13.1 microg/l vs. 22. 1 +/- 9.8 microg/l; P = 0.01) and by AUC (450.0 +/- 361.3 microg/l vs. 672.3 +/- 393.0 microg/l; P = 0.002) was significantly decreased in CFS patients vs. controls. Nocturnal GH secretion assessed by GH peak value (5.4 +/- 3.7 vs. 9.0 +/- 5.1 microg/l; P = 0.44) and by AUC (34.4 +/- 20.2 vs. 67.4 +/- 43.1; P = 0.045) was also significantly impaired in CFS patients. Arginine and clonidine administration showed no differences in GH secretion between CFS patients and controls. In the CFS group, GH peak values were significantly higher after ITT than after arginine (P = 0.017) or clonidine (P = 0.001). No differences in serum IGF-I levels were found between CFS patients and controls. Except for a significantly lower nocturnal cortisol peak value, no differences were found in ACTH and cortisol secretion between CFS patients and controls. Significantly higher serum prolactin levels (7.4 +/- 4.7 microg/l vs. 4.4 +/- 1.3 microg/l; P = 0.004) and significantly higher serum TSH levels (1.6 +/- 1.0 mU/l vs. 1.0 +/- 0.4 mU/l; P = 0.011) were found in CFS patients. Serum free thyroxine was comparable in both groups. Visceral fat mass was significantly higher in CFS patients (86.6 +/- 34.9 cm2 vs. 51.5 +/- 15.7 cm2; P < 0.001). CONCLUSIONS: We observed a significant impairment of GH response during insulin-induced hypoglycaemia and a low nocturnal GH secretion in CFS patients. These changes did, however, not lead to different concentrations in serum IGF-I. The clinical expression of this inadequate GH secretion can thus be questioned, although the alteration in body composition may be related to this relative GH deficiency. Significantly increased prolactin and TSH levels were found when compared to controls. These findings give support to the hypothesis of a decreased dopaminergic tone in CFS. Further investigations are required in order to identify specific adaptations within the neurotransmitter system in CFS and to determine the clinical importance of the impaired GH homeostasis.

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Title: Indirect evidence that estrogen replacement therapy stimulates nitric oxide synthase in postmenopausal women.
Source: Gynecol Endocrinol (GYNECOLOGICAL ENDOCRINOLOGY) 2000 Apr; 14 (2): 142-6 Journal Code: 125
Additional Info: ENGLAND
Standard No: ISSN: 0951-3590
Language: ENGLISH
Abstract: The aim of the study was to investigate the effects of estrogen replacement therapy (ERT) on nitric oxide (NO) activity in healthy postmenopausal women. The study group consisted of 22 postmenopausal women (last menses at least 12 months prior to study entry) who were randomized to receive treatment for 2 months with patches that delivered either 50 micrograms/day of 17 beta-estradiol or placebo in a cross-over design. Blood samples for measurements of serum citrulline and arginine were collected at the start of the study and at the end of each treatment course. Serum citrulline and arginine were measured using high-performance liquid chromatography with fluorometric detection. Arginine levels were significantly lower in the ERT group compared to the placebo group, while citrulline levels did not change. The percentage citrulline/arginine ratio was significantly higher in the ERT group (42.9 +/- 21.6) compared to the placebo group (33.9 +/- 18.5) ($p < 0.01$). The citrulline/arginine ratio, both at baseline and during either ERT or placebo administration demonstrated a positive linear correlation with body mass index (BMI). No correlations were found between follicle stimulating hormone, estradiol and insulin levels and BMI. No correlations were found between age, time since menopause and baseline arginine and citrulline levels or the citrulline/arginine ratio. These data indirectly demonstrate that transdermal estradiol replacement in postmenopausal women is able to stimulate NO production through the involvement of endogenous L-arginine. A positive linear correlation was found between BMI and the citrulline/arginine ratio, suggesting an additional protective cardiovascular effect in overweight women.

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Title: **Effect of GH and/or testosterone deficiency on the prostate: an ultrasonographic and endocrine study**

in GH-deficient adult patients.

Source: Eur J Endocrinol (EUROPEAN JOURNAL OF ENDOCRINOLOGY) 2000 Jul; 143 (1): 61-9 Journal Code: BXU

Additional Info: ENGLAND

Standard No: ISSN: 0804-4643

Language: ENGLISH

Abstract: BACKGROUND: The role of IGF-I in prostate development is currently under thorough investigation since it has been claimed that IGF-I is a positive predictor of prostate cancer. OBJECTIVE: To investigate the effect of chronic GH and IGF-I deficiency alone or associated with testosterone deficiency on prostate pathophysiology in a series of patients with hypopituitarism. DESIGN: Pituitary, androgen and prostate hormonal assessments and transrectal prostate ultrasonography (TRUS) were performed in 30 men with adulthood onset GH deficiency (GHD) and 30 age-matched healthy controls, free from previous or concomitant prostate disorders. RESULTS: Plasma IGF-I levels were significantly lower in GHD patients than in controls (Pearson's coefficient P<0.0001). At study entry, 6 of the 13 hypogonadal patients and 7 of the 17 eugonadal patients had plasma IGF-I below the age-adjusted normal range. At study entry, testosterone levels were low in 13 patients (mean +/-s.e.m., 3.8+/-1.0 nmol/l) while they were normal in the remaining 17 (19.4+/-1.4 nmol/l). No difference in prostate-specific antigen (PSA), and PSA density was found between GHD patients (either hypo- or eugonadal) and controls, while free PSA levels were significantly higher in eugonadal GHD than in controls (0.4+/-0.04 vs 0.2+/-0.03 microg/l; P<0.01). No difference in antero-posterior prostate diameter and transitional zone volume (TZV) was observed among groups, while both transverse and cranio-caudal diameters were significantly lower in hypogonadal (P<0.01) and eugonadal GHD patients (P<0.05) than in controls. Prostate volume (PV) was significantly lower in hypogonadal GHD patients (18.2+/-3.0 ml) and eugonadal GHD patients (22.3+/-1.6 ml), than in controls (25.7+/-1.4, P<0.05). The prevalence of prostate hyperplasia (PV>30 ml) was significantly lower in hypogonadal and eugonadal GHD patients, without any difference between them (15.3% and 5.8%), than in controls (43.3%) (chi(2)=6.90, P=0.005). No difference was found in PV between patients with normal or deficient IGF-I levels both in the hypogonadal group (19. 9+/-4.7 vs 17.3+/-4.0 ml) and in the eugonadal group (22.6+/-2.3 vs 21.8+/-2.5 ml). When controls and patients were

divided according to age (<60 years and >60 years), PV was significantly lower in hypogonadal GHD patients aged below 60 years than in age-matched controls (P<0.01) or eugonadal GHD patients (P<0.01), without any difference between controls and eugonadal GHD patients. Controls aged above 60 years had significantly higher PV than both hypogonadal and eugonadal GHD patients (P<0.01). Calcifications, cysts or nodules were found in 56.7% of patients and in 50% of controls (chi(2)=0.067, P=0.79). In controls, but not in GHD patients, PV and TZV were correlated with age (r=0.82, r=0.46, P<0. 0001 and P<0.01 respectively). PV was also correlated with GH (r=-0. 52, P=0.0026), IGF-I (r=-0.62, P=0.0002) and IGF-binding protein 3 (IGFBP-3) levels (r=-0.39, P=0.032) but neither with testosterone or dihydrotestosterone (DHT) levels. In GHD patients TZV but not PV was correlated with age (r=0.58, P=0.0007) and neither TZV nor PV were correlated with GH, IGF-I or IGFBP-3 levels. CONCLUSIONS: Chronic GH deficiency in adulthood causes a decrease in prostate size, mostly in patients with concomitant androgen deficiency and age below 60 years, without significant changes in the prevalence of structural prostate abnormalities.

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Title: **Comparisons among old and new provocative tests of GH secretion in 178 normal adults.**

Source: Eur J Endocrinol (EUROPEAN JOURNAL OF ENDOCRINOLOGY) 2000 Apr; 142 (4): 347-52 Journal Code: BXU

Additional Info: ENGLAND

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Abstract: Classical provocative stimuli of GH secretion such as insulin-induced hypoglycaemia, arginine, clonidine, glucagon and levodopa have been widely used in clinical practice for approximately 30 years. On the other hand, in the last 10 years new potent stimuli of GH secretion have been proposed, but an extensive comparison with the classical ones has rarely been performed, at least in adults. In order to compare the GH-releasing activity of old and new provocative stimuli of GH secretion, and to define the normative values of the GH response, in 178 normal adults (95 males, 83 females; age range:

20-50 years, all within +/-15% of their ideal body weight), we studied the GH response to: insulin-induced hypoglycaemia (ITT, 0.1IU/kg i.v.), arginine (ARG, 0.5g/kg i.v.), clonidine (CLO, 300 microg/kg p.o.), glucagon (GLU, 1mg i.m.), pyridostigmine (PD, 120mg p.o.), galanin (GAL, 80pmol/kg per min), GH-releasing hormone (GHRH, 1 microg/kg i.v.), GHRH+ARG, GHRH+PD, hexarelin, a GH-releasing protein (HEX, 2 microg/kg i.v.) and GHRH+HEX (0.25 microg/kg i.v.). The mean (+/-s.e.m.) peak GH response to ITT (21.8+/-2.8, range: 3.0-84.0 microg/l) was similar to those to ARG (18.0+/-1.6, range: 2.9-39.5 microg/l) or GLU (20. 5+/-2.2, range: 10.6-36.9 microg/l) which, in turn, were higher (P<0. 001) than those to CLO (8.2+/-1.6, range: 0.3-21.5 microg/l), PD (9. 6+/-1.1, range: 2.2-33.0 microg/l) and GAL (9.3+/-1.1, range: 3.9-18. 3 microg/l). The GH response to GHRH (19.1+/-1.5, range: 2.7-55.0 microg/l) was similar to those after ITT, ARG or GLU but clearly lower than those after GHRH+ARG (65.9+/-5.5, range: 13.8-171.0 microg/l) and GHRH+PD (50.2+/-4.6, range: 17.7-134.5 microg/l) which, in turn, were similar. The GH response to HEX (55.3+/-5.5, range: 13.9-163.5 microg/l) was similar to those after GHRH+ARG and GHRH+PD but lower (P<0.001) than that after GHRH+HEX (86.0+/-4.3, range: 49. 0-125.0 microg/l) which was the most potent stimulus of GH secretion. In this adult population the third centile limits of peak GH response to various stimuli were the following: ITT: 5.3; ARG: 2.9; CLO: 1.5; GLU: 7.6; PD: 2.2; GAL: 4.0; GHRH: 5.0; GHRH+ARG: 17.8; GHRH+PD: 17.9; HEX: 21.6; GHRH+HEX: 57.1. These results confirm that, among classical provocative tests of GH secretion, ITT followed by ARG and GLU are the most potent ones and possess clear limits of normality. GHRH+ARG or PD and HEX are strong stimuli of GH secretion which, however, is maximally stimulated by a combination of GHRH and a low dose of HEX. It is recommended that each test is used with appropriate cut-off limits.

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Title: **Reduction of the pituitary GH releasable pool in short children with GH neurosecretory dysfunction.**
Source: Clin Endocrinol (Oxf) (CLINICAL ENDOCRINOLOGY) 2000

Mar; 52 (3): 287-93
Abstract: OBJECTIVES: The classical 'GH neurosecretory dysfunction' (GHNSD) refers to slowly growing children with normal GH responses to classical provocative tests but impaired spontaneous GH secretion over 24 h frequently leading to low IGF-I levels. Thus it has been assumed that these subjects have insufficiency of spontaneous GH secretion due to neuroendocrine abnormalities in spite of a normal releasable pool of GH. However, classical provocative tests do not reliably assess the maximal somatotroph capacity; thus it is still unclear if the GH pool is really preserved or not. GHRH + arginine test is more potent than the classical tests and evaluates the maximal secretory capacity of somatotroph cells. The GH response to this stimulus is reproducible and also independent of age and puberty. DESIGN AND PATIENTS: We studied the GH response to GHRH (1 microgram/kg iv) + arginine (ARG, 0.5 g/kg iv) in 19 short children with GHNSD (14 boys and 5 girls, age: 12.1 +/- 0.7 years, pubertal stages I-III, HV-SDS between -1.6 and -4.9; GH peak > 10 micrograms/l after classical stimuli but mean GH concentration (mGHc) < 3 micrograms/l). The results in GHNSD were compared with those in 38 short children with idiopathic or organic severe GHD (GHD, 29 boys and 9 girls, age: 11.2 +/- 0.6 years, pubertal stages I-III, HV-SDS between -1.8 and -4.4; GH peak < 10 micrograms/l after 2 classical provocative tests) and in 83 children with normal or familial short stature (NC, 59 boys and 24 girls, age: 11.5 +/- 0.3 years., pubertal stages I-III; HV-SDS > 25th centile, normal IGF-I levels). RESULTS: Mean IGF-I levels in GHNSD (121.9 +/- 20.3 micrograms/l) were lower (P < 0.001) than those in NC (270.3 +/- 13.8 micrograms/l) but higher (P < 0.001) than those in GHD (72.0 +/- 4.0 micrograms/l). The mean GH concentration (mGHc) in GHNSD (2.1 +/- 0.1 micrograms/l) was lower (P < 0.01) than that in NC (4.9 +/- 0.5 micrograms/l) but higher (P < 0.01) than that in GHD (1.5 +/- 0.2 micrograms/l). On the other hand, the mean peak GH response to GHRH + ARG in GHNSD (43.7 +/- 3.7 micrograms/l) was markedly higher (P < 0.001) than that in GHD (8.2 +/- 0.9 micrograms/l) but significantly lower (P < 0.01) than that in NC (60. 4 +/- 2.7 micrograms/l). All GHD patients had peak GH responses to GHRH + ARG below the 3rd centile limit of normality (20 micrograms/l), while all GHNSD patients had peak GH responses within the normal range. No significant correlation was found between GH peak after GHRH + ARG, mGHc and IGF-I levels in each group.

CONCLUSION: Our study demonstrates that short children with 'GH neurosecretory dysfunction' show reduction in the GH releasable pool evaluated by the provocative and potent GHRH + arginine test. However, the peak GH response to a single GHRH + arginine test in GH neurosecretory dysfunction is always within the normal range indicating that this test as well as classical stimuli does not distinguish normal subjects from GH neurosecretory dysfunction.

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Title: **Growth hormone (GH) status is an independent determinant of serum levels of cholesterol and triglycerides in healthy adults.**
Source: Clin Endocrinol (Oxf) (CLINICAL ENDOCRINOLOGY) 1999 Sep; 51 (3): 309-16
Abstract: OBJECTIVE: Both severe growth hormone (GH) deficiency in hypopituitary adults and physiological ageing are associated with an increase in fat mass, dyslipidaemia, and an increased incidence of cardiovascular disease. Ageing is also associated with a physiological decrease in spontaneous as well as stimulated GH secretion. We wished to evaluate the effects of endogenous GH status on circulating lipoproteins. DESIGN: A cross-sectional study. SUBJECTS: Forty-two healthy nonobese adults of both sexes (20 M + 22 F) aged 27-59 years. MEASUREMENTS: Twenty-four hour GH secretion, arginine-stimulated GH secretion, and fasting values of lipoproteins and triglycerides. Body composition was measured by CT-scan and whole body DXA-scan. VO2-max was measured on an ergometer bicycle. RESULTS: GH secretion decreased with age and was lower in males. Older subjects had more total body fat, subcutaneous abdominal fat, and intra-abdominal fat than younger ones, and their VO2-max was decreased. Men had more intra-abdominal and subcutaneous abdominal fat but less total body fat than women. There was no sex difference in VO2-max. Total cholesterol (TC) and LDL-C (mmol/l) were higher in older than in the younger subjects (TC: 5.32 (95% CI = 0.49) vs. 4. 17 (95% CI = 0.28), P < 0.001; LDL-C: 3.66 (95% CI = 0.52) vs. 2.54 (95% CI = 0.37), P = 0.001) without sex differences. HDL-C did not show any difference with age or between sexes. Triglycerides (mmol/l) were higher in older subjects and in males (older: 1.36 (95% CI = 0.19)

vs. younger: 1.02 (95% CI = 0.20), P = 0.015; M: 1. 34 (95% CI = 0.24) vs. F: 1.03 (95% CI = 0.16), P = 0.03). There was no age-difference in lipoprotein (a), but concentrations were higher in women (M: 4.35 (2.95-8.30) vs. F: 19.40 (4.10-32.80), P = 0.03). TC, LDL-C, and triglycerides correlated positively with age and indices of adiposity, and inversely with VO2-max. TC, LDL-C, and triglycerides also correlated significantly and negatively with arginine-stimulated GH secretion (peak GH) (TC vs. peak GH (r = - 0. 395, P = 0.01); LDL-C vs. peak GH (r = - 0.365, P = 0.017); triglycerides vs. peak GH (r = - 0.386, P = 0.01)). Multiple linear regression analysis showed GH status to be an independent predictor of both TC, LDL-C, and triglycerides. CONCLUSION: We hypothesize that GH may exert direct effects on lipid metabolism.

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Title: **Growth hormone status following treatment for Cushing's syndrome**.
Source: Clin Endocrinol (Oxf) (CLINICAL ENDOCRINOLOGY) 1999 Jul; 51 (1): 61-6 Journal Code: DCI
Additional Info: ENGLAND
Standard No: ISSN: 0300-0664
Language: ENGLISH
Abstract: OBJECTIVE: Both pituitary surgery and radiotherapy for Cushing's disease can lead to growth hormone (GH) deficiency. Studies to date have, however, described the incidence of impaired GH secretion and not the incidence of severe GH deficiency following treatment of Cushing's disease. Furthermore, following cure of Cushing's disease and resolution of hypercortisolaemia, recovery of GH secretory status is seen, thus creating uncertainty as to the persistence of any documented GH deficiency. This study has two aims; to determine the incidence of severe persistent GH deficiency following treatment of Cushing's disease and to assess the time scale of any recovery of GH secretory status following surgical cure of Cushing's disease. DESIGN AND PATIENTS: The case notes of 37 patients either cured or in clinical and biochemical remission following treatment for Cushing's syndrome were reviewed to determine the incidence of severe GH deficiency. Of 34 patients with Cushing's disease, 20 were treated by pituitary surgery, and 14 with radiotherapy. Three patients with adrenal adenomas underwent unilateral adrenalectomy. MEASUREMENTS: GH secretory status was assessed by provocative testing using an

insulin tolerance test (ITT, 85% of all tests), glucagon stimulation test (GST) or arginine stimulation test (AST). RESULTS: Thirty-six percent (5/14) of radiotherapy treated patients demonstrated severe GH deficiency at a mean time of 99 months following remission. Fifty-nine percent (10/17) of surgically treated patients assessed in the two years following remission demonstrated severe GH deficiency, whilst only 22% (2/9) of patients assessed beyond two years following remission demonstrated severe GH deficiency. This latter cohort is biased, with patients in whom severe GH deficiency had been demonstrated on earlier tests being over-represented. It is more accurate to estimate the incidence of persistent severe GH deficiency following surgically induced remission of Cushing's disease by incorporating data from patients in whom original testing demonstrated adequate GH reserve. Collating such data, 13% (2/15) of patients had persistent severe GH deficiency. Across all time periods five surgically treated patients demonstrated recovery of GH secretory status over a median time course of 19 months. In the surgically treated cohort, seven (35%) patients had anterior pituitary hormone deficits other than GH deficiency: 14% (2/14) of patients with normal GH secretory status at the last assessment, 83% (5/6) of patients with severe GHD at the last assessment. Of the 5 patients who demonstrated recovery of GH secretory status 40% (2) had additional anterior pituitary hormone deficits. Within the radiotherapy treated cohort 14% (2/14) of patients demonstrated additional anterior pituitary hormone deficits: 11% (1/9) of patients with normal GH secretory status and 20% (1/5) of patients with severe GH deficiency. None of the patients with adrenal adenomas treated by unilateral adrenalectomy demonstrated any abnormality of GH secretory status CONCLUSIONS: The incidence of severe persistent GH deficiency following surgically induced or radiotherapy induced remission of Cushing's disease is lower than has been suggested by previous studies, although these latter studies have assessed GH insufficiency and not severe GH deficiency. In the presence of additional pituitary hormone deficits severe GHD is common and is likely to be persistent. Recovery of GH secretory status is seen in a high proportion of patients reassessed, at a median time of 19 months following surgically induced remission of Cushing's disease. Thus, we recommend that definitive assessment of GH secretory status is delayed for at least two years

following surgical cure of Cushing's disease. This has important implications for patients in whom GH replacement therapy is being considered.

Author(s): Lissett CA ; Thompson EG ; Rahim A ; Brennan BM ; Shalet SM
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Title: **How many tests are required to diagnose growth hormone (GH) deficiency in adults?**
Source: Clin Endocrinol (Oxf) (CLINICAL ENDOCRINOLOGY) 1999 Nov; 51 (5): 551-7 Journal Code: DCI
Additional Info: ENGLAND
Standard No: ISSN: 0300-0664
Language: ENGLISH
Abstract: OBJECTIVE: The diagnosis of GH deficiency in adults relies on the results of GH provocative testing. Whilst in some patients the testing strategy is clear, this is not the case in all patients. The objective of this study was to further examine the concordance between the GH responses to two different provocative stimuli, to correlate this with the number of additional pituitary hormone deficits, and to produce guidelines as to which patients require two GH provocative tests and which require only one. STUDY DESIGN AND PATIENTS: The results of GH provocative tests were reviewed in 103 patients (mean age 28 years, 48 male), with documented or potential hypothalamic-pituitary disease and 35 normal volunteers (mean age 21 years, 18 male). All patients and normal volunteers underwent an insulin tolerance test (ITT) and an arginine stimulation test (AST). Severe GH deficiency was defined as a GH response to an ITT of < 5 mU/l and a GH response to an AST of < 2 mU/l, utilizing data from previous studies in this unit. Patients were divided into four groups according to the number of anterior pituitary hormone deficits present other than possible GH deficiency: no other pituitary hormone deficits (GHD0) or one, two or three other hormone deficits (GHD1, GHD2 or GHD3). RESULTS: The 103 patients were divided between the four groups as follows: 69 (67%) in GHD0, 15 (14. 6%) in GHD1, six (5.8%) in GHD2, and 13 (12.6%) in GHD3. There was a significant decline in the median GH peak to both the ITT and the AST with increasing numbers of other pituitary hormone deficits ($P < 0.0001$). If the magnitude of the difference between each individual's GH response to the ITT and AST is plotted against the mean GH value a clear trend is seen (Spearmans rank correlation = 0. 88, $P < 0.0001$) indicating that the magnitude of the

difference between the GH responses to an ITT and AST increases with the underlying mean GH value. These data allow the estimation of the median ITT/AST ratio as 1.17 (CI 0.98, 1.39). None of the control subjects and 14.1% (10), 26.7% (four), 83% (five) and 92.3% (12) of groups GHD0, 1, 2 and 3, respectively, had severe GHD. The concordance between the AST and ITT (percent of patients in whom both tests confirmed or refuted the biochemical diagnosis of severe GHD) was 100%, 76.8%, 66.6%, 83.3%, and 92.3% in the controls, GHD0, 1, 2, and 3, respectively. Thus, 16/69 GHD0, 5/15 GHD1, 1/6 GHD2 and 1/13 GHD3 patients were misclassified by one or other test. CONCLUSION: We have demonstrated that a constant ratio links the GH response to an ITT and AST in an individual, rather than a constant difference, and that the difference between the GH responses to two provocative stimuli is greater in those patients with milder degrees of GH deficiency or insufficiency. These patients tend to have one or no additional pituitary hormone deficits and may be misclassified if a single GH provocative test is performed. We suggest that whilst a single GH provocative test can be used with confidence in patients with two or three additional pituitary hormone deficits, in patients with suspected isolated GH deficiency or with only one additional pituitary hormone deficit, two GH provocative tests should be performed.

Descriptor: Arginine -- Diagnostic Use
Hypopituitarism -- Diagnosis
Insulin -- Diagnostic Use
Pituitary Gland -- Physiopathology
Somatotropin -- Deficiency
Adult
Case-Control Studies
Middle Age
Predictive Value of Tests
Female
Human
Male

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Title: **Patients with dilated cardiomyopathy show reduction of the somatotroph responsiveness to GHRH both alone and combined with arginine.**

Source: Eur J Endocrinol (EUROPEAN JOURNAL OF ENDOCRINOLOGY) 2000 Feb; 142 (2): 157-63

Abstract: OBJECTIVE: Altered function of the GH/IGF-I axis in patients with dilated cardiomyopathy (DCM) has been reported. In fact, DCM patients show reduction of IGF-I levels, which could reflect slight peripheral GH resistance or, alternatively, reduced somatotroph secretion. Spontaneous GH secretion has been reported to be altered by some but not by other authors, whereas the GH response to GHRH, but not that to GH-releasing peptides, seems reduced in DCM patients. On the other hand, it is well known that the GH response to GHRH in humans is markedly potentiated by arginine (ARG), which probably acts via inhibition of hypothalamic somatostatin release; in fact the GHRH+ARG test is known as one of the most reliable to evaluate the maximal secretory capacity of somatotroph cells. METHODS: In order to further clarify the somatotroph function in DCM, in well-nourished patients with DCM (34 male, 4 female; age (mean+/-s.e. m.) 57.8+/-1.1 years; body mass index (BMI) 24.6+/-0.6kg/m(2); left ventricular ejection fraction 23.2+/-1.6%; New York Heart Association classification I/1, II/17, III/18, IV/2) we studied the GH response to GHRH (1.0 microgram/kg i.v.) alone or combined with ARG (0.5g/kg i.v.). The results in DCM patients were compared with those in age-matched control subjects (CS) (39 male, 7 female; age 58.9+/-1.0 years; BMI 23.2+/-0.3kg/m(2)). RESULTS: Mean IGF-I levels in DCM patients were lower than in CS (144.3+/-6.9 vs 175.1+/-8. 4 microgram/l, P<0.05) whereas basal GH levels were similar in both groups (1.7+/-0.3 vs 1.7+/-0.3 microgram/l). The GH response to GHRH in DCM patients was lower (P<0.05) than that in CS (GH peak 6.5+/-1.2 vs 10.7+/-2.1 microgram/l). In both groups the GH response to GHRH+ARG was higher (P<0.001) than that to GHRH alone. However, the GH response to GHRH+ARG in DCM patients remained clearly lower (P<0.01) than that in CS (18.3+/-3.2 vs 34.1+/-4.6 microgram/l). The GH response to GHRH alone and combined with ARG was not associated with the severity of the disease. CONCLUSION: DCM patients show blunted GH responses to GHRH both alone and combined with ARG. Evidence that ARG does not restore the GH response to GHRH in DCM patients makes it unlikely that the somatotroph hyporesponsiveness to the neurohormone reflects hyperactivity of hypothalamic somatostatinergic neurons.

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Title: **Growth hormone (GH) responses to GH-releasing hormone alone or combined with arginine in patients with adrenal incidentaloma: evidence for enhanced somatostatinergic tone.**

Source: J Clin Endocrinol Metab (JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM) 2000 Mar; 85 (3): 1310-5 Journal Code: HRB

Additional Info: UNITED STATES

Standard No: ISSN: 0021-972X

Language: ENGLISH

Abstract: Spontaneous and stimulated GH secretion is blunted in hypercortisolemic states due to increased hypothalamic somatostatinergic tone. However, no data are available on the characteristics of GH secretion in patients with incidentally discovered adrenal adenomas. They represent an interesting model for studying GH secretion, as a slight degree of cortisol excess may frequently be observed in such patients who do not present with any clear Cushingoid sign. In the present study, 10 patients (3 men and 7 women, aged 48-63 yr) with an adrenal mass discovered serendipitously underwent, on separate occasions, a GHRH injection alone or combined with an infusion of the functional somatostatin antagonist, arginine. Thirteen age-matched healthy volunteers served as controls. Briefly, arginine (30 g) was infused from -30 to 0 min, and GHRH (100 microg) was injected as a bolus at 0 min, with measurement of serum GH [immunoradiometric assay (IRMA)] every 15 min for 150 min. Plasma IGF-I (RIA after acid-ethanol extraction) was measured in a morning sample. The diagnosis of cortical adenoma was based on computed tomography features and pattern of uptake on adrenal scintigraphy. Patients with obesity and/or diabetes were excluded. The study design included also an endocrine work-up aimed to study the hypothalamic-pituitary-adrenal axis [urinary free cortisol (UFC) excretion, serum cortisol at 0800 h, plasma ACTH at 0800 h, morning cortisol after overnight 1 mg dexamethasone]. Five of 10 patients showed abnormalities of the hypothalamic-pituitary-adrenal axis, including borderline or increased UFC excretion in 4 of them accompanied by blunted ACTH in 2 cases and failure of cortisol to suppress after dexamethasone in 1; the fifth patient displayed low ACTH and resistance to dexamethasone suppression. However, all patients had a unilateral uptake of the tracer on the side of the mass with suppression of the contralateral

normal adrenal gland. As a group, the patients displayed greater UFC excretion and lower ACTH concentrations than the controls. GH release after GHRH treatment was blunted in patients bearing adrenal incidentaloma compared with controls (GH peak, 5.7 +/- 5.2 vs. 18.0 +/- 7.0 microg/L; P < 0.0001), whereas GHRH plus arginine was able to elicit a comparable response in the 2 groups (GH peak, 33.5 +/- 20.3 vs. 33.7 +/- 17.5 microg/L; P = NS). The ratio between GH peaks after GHRH plus arginine and after GHRH plus saline was significantly greater in patients than in controls (751 +/- 531% vs. 81 +/- 45%; P = 0.0001). Similar data were obtained when comparing GH area under the curve after GHRH plus saline or GHRH plus arginine between the 2 groups. In summary, the present data suggest that in patients with incidental adrenal adenomas the GH response to GHRH is blunted due to increased somatostatinergic tone, as it can be restored to normal by pretreatment with the functional somatostatin antagonist arginine. The blunted GH release to GHRH may be an early and long lasting sign of autonomous cortisol secretion by the adrenal adenoma.

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Title: **Circulating insulin inhibits glucagon secretioninduced by arginine in type 1 diabetes.**
Source: Eur J Endocrinol (EUROPEAN JOURNAL OF ENDOCRINOLOGY) 2000 Jan; 142 (1): 30-4 Journal Code: BXU
Additional Info: ENGLAND
Standard No: ISSN: 0804-4643
Language: ENGLISH
Abstract: OBJECTIVE: To evaluate if insulin has a suppressive effect on the glucagon secretion stimulated by arginine in type 1 diabetes. RESEARCH DESIGN AND METHODS: The alpha-cell response to an i.v. bolus of arginine (150mgkg(-1)) followed by an infusion of arginine (10mgkg(-1)min(-1)) was studied in random order during either low dose infusion (LDT) or high dose infusion (HDT) of insulin in ten patients with type 1 diabetes. The blood glucose level was clamped at an arterialized level of 5mmoll(-1) by a variable infusion of glucose. Venous C-peptide, glucagon, growth hormone, and insulin were analyzed. RESULTS: The mean plasma concentration of insulin was four times higher during the HDT. The C-peptide level did not differ between the LDT and the HDT. During the LDT in

response to arginine the blood glucose level increased from 5.0 to 5.8mmol l(-1) although the glucose infusion was markedly reduced, while no change was seen during the HDT. A significantly smaller increase in the glucagon levels during the HDT was seen (area under the curve of 413+/-45 vs 466+/-44pgml(-1)h(-1), P=0.03) while the growth hormone levels were almost identical. CONCLUSION: This study demonstrates that a high level of circulating insulin exerts an inhibitory effect on the glucagon response to arginine in type 1 diabetes. Thus, the suppressive effect of insulin on the glucagon release from the alpha-cell seems to be general and not only dependent on stimulation by hypoglycemia.

Database: MEDLINE
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Title: **Arginine infusion and/or acute changes of growth hormone levels do not acutely alter leptin serum levels.**
Source: J Pediatr Endocrinol Metab (JOURNAL OF PEDIATRIC ENDOCRINOLOGY AND METABOLISM) 1999 Nov-Dec; 12 (6): 847-51 Journal Code: CEF
Additional Info: ENGLAND
Language: ENGLISH
Abstract: Leptin, the ob gene product, is produced by differentiated adipocytes. It functions as an afferent signal to the central nervous system indicating satiety and fat mass status. It acts upon the hypothalamic-pituitary axis. Growth hormone (GH) secretion is thought to be stimulated by leptin. Conversely, leptin secretion and ob gene expression are regulated by classical neuroendocrine networks. Whether or not acute changes of GH concentrations directly alter leptin serum levels in vivo is still debated. We investigated whether or not acute changes in GH serum concentrations during arginine infusion (0.5 g/kg b. wt.) alter leptin serum levels in 45 children and adolescents (33 M, 12 F). GH and leptin serum levels were determined at -30, 0, 30, 60, 90, 120 min after arginine infusion using specific radioimmunoassays. Leptin serum concentrations remained unaltered throughout the arginine infusion in all children and adolescents whether or not GH secretion was normal. In conclusion: (1) Acute changes of GH levels do not alter leptin serum levels during acute arginine infusions over 120 min. (2) Arginine does not acutely modulate leptin secretion.

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Title: **Hyperleptinaemia in young adults following cranial irradiation in childhood: growth hormone deficiency or leptin insensitivity?**
Source: Clin Endocrinol (Oxf) (CLINICAL ENDOCRINOLOGY) 1999 Feb; 50 (2): 163-9
Abstract: OBJECTIVE: In order to explore the mechanism of obesity in long-term survivors of childhood leukaemia, fat mass, lean body mass and serum leptin were assessed in a cohort of 32 (17 males) adults who had received cranial irradiation (XRT) in childhood as part of their treatment for acute lymphobiastic leukaemia (ALL), and compared with 35 age and body mass index (BMI) matched young adults (18 male). DESIGN: Thirty-one patients and 18 controls had fat mass and lean body mass assessed by dual x-ray absorptiometry (DEXA), using a lunar DPX-L scanner. Serum leptin concentrations were also measured in 27 patients and all controls. Growth hormone status had previously been determined using an insulin tolerance test and arginine stimulation test. Nine patients were classified as severe growth hormone (GH) deficient (group 1), 12 patients as GH insufficient (group 2) and 11 patients as normal (group 3). RESULTS: BMI and absolute fat mass were not significantly different between the patients and controls regardless of their gender ($P = 0.1$ and $P = 0.14$ respectively). In contrast, absolute lean mass was significantly reduced ($P < 0.01$) and leptin concentrations were significantly increased ($P < 0.001$) in patients compared with controls. BMI, fat mass and leptin concentrations but not lean mass were significantly different between the three GH status groups ($P < 0.01$, $P < 0.01$, $P = 0.004$, and $P = 0.67$ respectively). When leptin concentrations were expressed per unit of fat mass, they were increased in the patients compared with the controls ($P = 0.03$) with significant differences between the GH status groups ($P = 0.004$), being significantly higher in the severe GH deficient group. CONCLUSIONS: Young adults who receive cranial irradiation in childhood are prone to GH deficiency and hyperleptinaemia. The pathophysiological significance of the hyperleptinaemia remains to be established but it has occurred either as a consequence of radiation induced hypothalamic damage or GH deficiency.

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Title: **Influence of a species-specific extracellular amino acid on expression and function of the human gonadotropin-releasing hormone receptor.**

Source: Mol Endocrinol (MOLECULAR ENDOCRINOLOGY) 1999 Jun; 13 (6): 890-6 Journal Code: NGZ
Additional Info: UNITED STATES
Standard No: ISSN: 0888-8809
Language: ENGLISH

Abstract: The mammalian GnRH receptor is an atypical G protein-coupled receptor which lacks the C-terminal cytoplasmic tail that is present in all other seven-transmembrane domain receptors. The mouse and rat GnRH receptors contain 327 amino acids, whereas human, sheep, and bovine receptors have an additional residue in the second extracellular loop at position 191. Another notable species difference is that human receptors undergo agonist-induced internalization much more rapidly than the mouse receptor. In this report, the role of the additional amino acid (Lys191) in GnRH receptor function was studied in transiently expressed mutant and wild-type human and mouse GnRH receptors. Deletion of Lys191 from the human GnRH receptor caused a 4-fold increase in receptor expression in COS-1 and HEK 293 cells and a modest increase in binding affinity. The magnitude of the agonist-induced inositol phosphate response mediated by the deltaK191 human receptor was similar to that of the wild-type receptor, but the EC50 was decreased by about 5-fold. In addition, the rate of internalization of the deltaK191 human receptor was significantly reduced and was similar to that of the mouse receptor. In contrast to these effects of deletion of Lys191, its replacement by Arg, Glu, Gln, or Ala caused no significant change in receptor expression or function. These findings demonstrate that a specific residue in the extracellular region of the human GnRH receptor is a significant determinant of receptor expression, agonist-induced activation, and internalization.

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Title: Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism.

Source: J Clin Endocrinol Metab (JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM) 1999 Jun; 84 (6): 1919-24
Abstract: Reduced bone mineral density (BMD) has been reported in patients with isolated GH deficiency (GHD) or with multiple pituitary hormone deficiencies (MPHD). To investigate whether the severity of GHD was correlated with the degree of bone mass and turnover impairment, we evaluated BMD at the lumbar spine and femoral neck; circulating insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3), and osteocalcin levels, and urinary cross-linked N-telopeptides of type I collagen (Ntx) levels in 101 adult hypopituitary patients and 35 sex- and age-matched healthy subjects. On the basis of the GH response to arginine plus GHRH (ARG+/-GHRH), patients were subdivided into 4 groups: group 1 included 41 patients with a GH peak below 3 microg/L (0.9 +/- 0.08 microg/L), defined as very severe GHD; group 2 included 25 patients with a GH peak between 3.1-9 microg/L (4.7 +/- 0.4 microg/L), defined as severe GHD; group 3 included 18 patients with a GH peak between 9.1-16.5 microg/L (11.0 +/- 0.3 microg/L), defined as partial GHD; and group 4 included 17 patients with a GH peak above 16.5 microg/L (28.3 +/- 4.3 microg/L), defined as non-GHD. In all 35 controls (group 5), the GH response after ARG+/-GHRH was above 16.5 microg/L (40.7 +/- 2.2 microg/L). In patients in group 1, circulating IGF-I ($P < 0.001$), IGFBP-3 ($P < 0.05$), osteocalcin ($P < 0.001$), and urinary Ntx levels ($P < 0.001$) were lower than those in group 3-5, which were not different from each other; the t score at the lumbar spine (-1.99 +/- 0.2) and that at the femoral neck (-1.86 +/- 0.3) were lower than those in groups 3 (-0.5 +/- 0.7, $P < 0.01$ and -0.3 +/- 0.7, $P < 0.01$, respectively), 4 (-0.5 +/- 0.2, $P < 0.01$ and -0.3 +/- 0.7, $P < 0.01$, respectively), and 5 (-0.5 +/- 0.2, $P < 0.001$ and 0.0 +/- 0.02, $P < 0.001$, respectively). In patients in group 2, circulating IGF-I and IGFBP-3 levels were not different from those in group 1, whereas the t scores at the lumbar spine (-1.22 +/- 0.3) and femoral neck (-0.9 +/- 0.3) were significantly higher and lower, respectively, than those in groups 1 and 5 ($P < 0.05$) but not those in groups 3 and 4, and serum osteocalcin and urinary Ntx levels were significant higher than those in group 1 and lower than those in groups 3-5 ($P < 0.001$). To evaluate the effect of isolated GHD vs. MPHD, patients were subdivided according to the number of their hormonal deficits, such as panhypopituitarism

with (10 patients) or without (31 patients) diabetes insipidus, GHD with 1 or more additional pituitary deficit(s) (36 patients), isolated GHD (7 patients), 1-2 pituitary hormone deficit(s) without GHD (10 patients), and normal anterior pituitary function (7 patients). The t score at the lumbar spine and femoral neck and the biochemical parameters of bone turnover were not significantly different among the different subgroups with similar GH secretions. A significant correlation was found between the GH peak after ARG+GHRH and IGF-I, osteocalcin, urinary Ntx levels, and the t score at the lumbar spine, but not that at the femoral neck level. A significant correlation was also found between plasma IGF-I levels and the t score at the lumbar spine and femoral neck, serum osteocalcin, and urinary Ntx. Multiple correlation analysis revealed that the t score at the lumbar spine, but not that at the femoral neck, was more strongly predicted by plasma IGF-I levels ($t = 3.376$; $P < 0.005$) than by the GH peak after ARG+GHRH ($t = -0.968$; $P = 0.338$). In conclusion, a significant reduction of BMD associated with abnormalities of bone turnover parameters was found only in patients with very severe or severe GHD, whereas normal BMD values were found in non-GHD hypopituitary patients. These abnormalities were consistently present in all patients with GHD regardless of the presence of additional hormone deficits, suggesting that GHD plays a central role in the development of osteopenia in hypopituitary patients.

Author(s): Laursen EM ; Lanng S ; Rasmussen MH ; Koch C ; Skakkebaek NE ; MŸller J
Address: Department of Growth and Reproduction GR, State University Hospital, Rigshospitalet, Copenhagen, Denmark.
Title: **Normal spontaneous and stimulated GH levels despite decreased IGF-I concentrations in cystic fibrosis patients.**
Source: Eur J Endocrinol (EUROPEAN JOURNAL OF ENDOCRINOLOGY) 1999 Apr; 140 (4): 315-21 Journal Code: BXU
Additional Info: ENGLAND
Standard No: ISSN: 0804-4643
Language: ENGLISH
Abstract: OBJECTIVE: The aim of the present study was to investigate whether patients with cystic fibrosis (CF) are GH resistant with increased GH release and decreased concentrations of IGF-I as a result of malabsorption, increased catabolism and impaired glucose tolerance. DESIGN: Twenty CF patients were

included, ten with normal glucose tolerance (five male, five female, median age 25.5 years (range 20-31)) and ten with diabetes mellitus (five male, five female, median age 25.3 years (range 17-45). Twenty healthy individuals served as controls (ten male, ten female, median age 28.4 years (range 18-36)). METHODS: GH status was evaluated by 12h spontaneous GH release during the night time, arginine-stimulated GH release and the basal concentrations of IGF-I and insulin-like growth factor-binding protein-3 (IGFBP-3). Twelve hour spontaneous GH profiles were estimated using a constant blood withdrawal technique with sampling every 30min and the Pulsar method was used for the analysis of profiles. RESULTS: No significant differences were found in spontaneous and stimulated GH release in CF patients compared with healthy controls, whereas IGF-I and IGFBP-3 were significantly decreased in CF patients compared with healthy controls. The combination of reduced IGF-I and IGFBP-3 with normal GH release points to a relative GH resistance or a disturbance in the pituitary axis in patients with CF. The spontaneous GH release, the stimulated GH release and the basal concentrations of IGF-I and IGFBP-3 were not significantly different in diabetic CF patients compared with CF patients with normal glucose tolerance and the presence of diabetes mellitus was not consistent with increased GH resistance in CF patients. CONCLUSION: CF patients with normal glucose tolerance and diabetic CF patients had normal GH release and decreased concentrations of IGF-I indicating a relative GH resistance.

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Title: Hyperenterostatinemia in premenopausal obese women.

Source: J Clin Endocrinol Metab (JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM) 1999 Mar; 84 (3): 937-41 Journal Code: HRB

Additional Info: UNITED STATES

Standard No: ISSN: 0021-972X

Language: ENGLISH

Abstract: Enterostatins [Val-Pro-Asp-Pro-Arg (VPDPR), Val-Pro-Gly-Pro-Arg (VPGPR), and Ala-Pro-Gly-Pro-Arg (APGPR)] are pentapeptides derived from the NH2-terminus of procolipase after tryptic cleavage and belong to the family of gut-brain peptides. Although enterostatin-like

immunoreactivities exist in blood, brain, and gut, and exogenous enterostatins decrease fat appetite and insulin secretion in rats, the roles of these peptides in human obesity remain to be examined. To determine whether VPDPR and APGPR secretion is altered in obesity, serum VPDPR and APGPR levels were measured in 38 overnight-fasted subjects (body mass index, 17.9-54.7 kg/m2) before and after a meal. The mean fasting VPDPR in the serum of lean subjects was significantly lower than that in obese subjects [lean = 603 +/- 86 nmol/L (n = 17); obese, 1516 +/- 227 nmol/L (n = 21); P = 0.0023]. In addition, the rise in serum APGPR after a meal (postmeal/fasting ratio) was significantly higher in lean than in obese subjects [lean, 1.71 +/- 0.24 (n = 17); obese, 1.05 +/- 0.14 (n = 21); P = 0.0332]. The results of these studies show hyperenterostatinemia in obesity and a diminution in enterostatin secretion after satiety.

Author(s): Thams P ; Capito K
Address: Department of Medical Biochemistry and Genetics, Biochemistry Laboratory A, The Panum Institute, University of Copenhagen, Denmark.
Title: **L-arginine stimulation of glucose-induced insulin secretion through membrane depolarization and independent of nitric oxide.**
Source: Eur J Endocrinol (EUROPEAN JOURNAL OF ENDOCRINOLOGY) 1999 Jan; 140 (1): 87-93 Journal Code: BXU
Additional Info: ENGLAND
Standard No: ISSN: 0804-4643
Language: ENGLISH
Abstract: The mechanism of L-arginine stimulation of glucose-induced insulin secretion from mouse pancreatic islets was studied. At 16.7 mmol/l glucose, L-arginine (10 mmol/l) potentiated both phases 1 and 2 of glucose-induced insulin secretion. This potentiation of glucose-induced insulin secretion was mimicked by the membrane depolarizing agents tetraethylammonium (TEA, 20 mmol/l) and K+ (60 mmol/l), which at 16.7 mmol/l glucose obliterated L-arginine (10 mmol/l) modulation of insulin secretion. Thus L-arginine may potentiate glucose-induced insulin secretion by stimulation of membrane depolarization. At 3.3 mmol/l glucose, L-arginine (10 mmol/l) failed to stimulate insulin secretion. In accordance with membrane depolarization by the electrogenic transport of L-arginine, however, L-arginine (10 mmol/l) stimulation of insulin secretion was enabled by the K+ channel inhibitor TEA (20 mmol/l), which potentiates membrane depolarization

by L-arginine. Furthermore, L-arginine (10 mmol/l) stimulation of insulin secretion was permitted by forskolin (10 micromol/l) or tetradecanoylphorbol 13-acetate (0.16 micromol/l), which, by activation of protein kinases A and C respectively sensitize the exocytotic machinery to L-arginine-induced Ca2+ influx. Thus glucose may sensitize L-arginine stimulation of insulin secretion by potentiation of membrane depolarization and by activation of protein kinase A or protein kinase C. Finally, L-arginine stimulation of glucose-induced insulin secretion was mimicked by NG-nitro-L-arginine methyl ester (10 mmol/l), which stimulates membrane depolarization but inhibits nitric oxide synthase, suggesting that L-arginine-derived nitric oxide neither inhibits nor stimulates insulin secretion. In conclusion, it is suggested that L-arginine potentiation of glucose-induced insulin secretion occurs independently of nitric oxide, but is mediated by membrane depolarization, which stimulates insulin secretion through protein kinase A- and C-sensitive mechanisms.

OPTHAMOLOGY

Author(s): Fletcher EL
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Title **Alterations in neurochemistry during retinal degeneration**.
Source: Microsc Res Tech (MICROSCOPY RESEARCH AND TECHNIQUE) 2000 Jul 15; 50 (2): 89-102
Abstract: Retinitis pigmentosa refers to a family of hereditary retinal degenerations that lead to photoreceptor death and vision loss. The underlying cause(s) are not known. In recent years there has been accumulating evidence of neurochemical changes during degeneration. In particular, the amino acids glutamate, GABA, and glycine show alterations in labelling intensity in subsets of neurons. Furthermore, there are differences in the labelling of the precursors, glutamine and aspartate, prior to, during, and following loss of photoreceptors, suggesting that the metabolic pathways involved in neurotransmitter formation and degradation may be abnormal. In addition, there is an elevation in glutamine and arginine content within MŸller cells prior to the onset of photoreceptor death. Investigations evaluating MŸller cell function indicate that formation and degradation of glutamate, in particular, is abnormal in the degenerating retina from an early age. These studies suggest that even though the primary

genetic defect of the RCS rat is within the retinal pigment epithelium, MŸller cells develop abnormally, and may contribute to the observed photoreceptor loss. Copyright 2000 Wiley-Liss, Inc.

Author(s): NSnto-Salonen K ; Komu M ; Lundbom N ; HeinSnen K ; Alanen A ; SipilS I ; Simell O
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Title: **Reduced brain creatine in gyrate atrophy of the choroid and retina with hyperornithinemia [see comments]**
Source: Neurology (NEUROLOGY) 1999 Jul 22; 53 (2): 303-7
Abstract: OBJECTIVE: To analyze in vivo brain creatine (Cr) content in gyrate atrophy of the choroid and retina with hyperornithinemia (GA). BACKGROUND: GA is caused by inherited deficiency of ornithine-delta-aminotransferase activity. Patients lose their vision by middle age and develop selective atrophy of type II skeletal muscle fibers. As demonstrated by MRS, the patients' skeletal muscles have diminished stores of high-energy Cr phosphate. Minor structural and electrophysiologic abnormalities in the brain of these patients also imply that the CNS may be affected. METHODS: The authors acquired proton MR spectra of the basal ganglia of 22 healthy control subjects and 20 GA patients. Nine patients received supplementary Cr or its precursors, and one child was on an arginine-restricted diet to normalize plasma ornithine concentration. The ratios of N-acetylaspartate (NAA) to Cr, NAA to choline (Cho), and Cho to Cr, and the ratios of NAA, Cho, and Cr to tissue water were calculated. RESULTS: NAA/Cr (Cho/Cr) in the untreated and treated patients and control subjects were (mean +/- SD) 3.3+/-0.4, 2.0+/-0.4, and 1.5+/-0.7 (1.9+/-0.3, 1.3+/-0.4, and 0.9+/-0.2), indicating that Cr content in untreated GA patients was proportionally and markedly diminished, and partially corrected by therapy ($p < 0.0001$). NAA/Cho was similar in all three groups. Cr/water in the untreated patients was only 46%, and increased to 75% of the control ratios in the treated patients ($p < 0.0001$). CONCLUSIONS: Hyperornithinemia-associated Cr deficiency in GA also affects the CNS, further supporting the possibility that Cr deficiency also has a pathogenetic role in the retina. The deficiency was partially corrected by Cr supplementation and an arginine-restricted diet.

Author(s): Farboud B ; Aotaki-Keen A ; Miyata T ; Hjelmeland LM ; Handa JT
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Davis, CA, 95616-8794, USA.
Title: **Development of a polyclonal antibody with broad epitope specificity for advanced glycation endproducts and localization of these epitopes in Bruch's membrane of the aging eye.**
Source: Mol Vis (MOLECULAR VISION) 1999 Jul 14; 5: 11
Abstract: PURPOSE: To develop an antibody that recognizes a variety of advanced glycation endproduct (AGE) epitopes. METHODS: Glycolaldehyde was used to modify bovine serum albumin and HPLC analysis was used to measure pentosidine formation as an indicator of AGE formation. A polyclonal anti-AGE antibody was synthesized by injecting glycolaldehyde-incubated keyhole limpet hemocyanin into rabbits, affinity purified using AGE modified bovine serum albumin coupled to an affinity resin column, and characterized by immunoblot analysis. RESULTS: HPLC analysis of glycolaldehyde treated bovine serum albumin detected high levels of pentosidine formation, suggesting that glycolaldehyde is a potent precursor for pentosidine. By immunoblot analysis, our antibody recognized carboxymethyllysine and pentosidine, two well-characterized AGEs, as well as other AGE epitopes. Immunohistochemical evaluation showed evidence of AGEs in Bruch's membrane (including basal laminar deposits and drusen), choroidal extracellular matrix, and vessel walls in an 82 year old nondiabetic globe. A similar staining pattern was observed in an age-matched diabetic control. In contrast, no staining was seen with the antibody in a 20 month old nondiabetic globe. CONCLUSIONS: A unique anti-AGE antibody was synthesized that recognizes a variety of AGE epitopes including carboxymethyllysine and pentosidine. Its best use might be in broad surveys of the age-dependent accumulation of a large number of AGE epitopes that might not be revealed by antibodies to pentosidine or CML.

Author(s): Baer CA ; Van Niel EE ; Cronk JW ; Kinter MT ; Sherman NE ; Braiman MS ; Gonzalez-Fernandez F
Address: Graduate Program in Neuroscience, University of Virginia Health Sciences Center, Charlottesville, VA 22906-0009, USA.
Title: **Arginine to glutamine substitutions in the fourth module of Xenopus interphotoreceptor retinoid-binding protein.**
Source: Mol Vis (MOLECULAR VISION) 1998 Dec 30; 4: 30
Abstract: PURPOSE: Interphotoreceptor retinoid-binding protein (IRBP) is unusual for a lipid-binding protein in that its gene is expressed uniquely by cells of photoreceptor origin and consists of four homologous repeats, each coding for a module of

approximately 300 amino acid residues. All-trans retinol binding domains, which appear to be present in each module, are composed of conserved hydrophobic regions [Baer et al, Exp Eye Res 1998; 66:249-262]. Here we investigate the role of highly conserved arginines contained in these regions. METHODS: To study the arginines in an individual module without the interference of ligand-binding activity elsewhere in the protein, we expressed in E. coli the fourth module of Xenopus IRBP by itself as a soluble thioredoxin fusion protein (X4IRBP). Arginines 1005, 1041, 1073 and 1122 were separately replaced by glutamine using PCR overlap extension mutagenesis. The glutamine substitutions were confirmed by liquid chromatography-tandem mass spectrometry. The binding of all-trans retinol and 9-(9-anthroyloxy)stearic acid (9-AS) to X4IRBP and each of the mutants was evaluated by fluorescence spectroscopy. Binding was followed by monitoring the enhancement of ligand fluorescence and the quenching of protein endogenous fluorescence. The ability of the recombinant proteins to protect all-trans retinol from oxidative degradation was evaluated by monitoring absorbance at 325 nm over time. RESULTS: The substitution of Gln for Arg1005 about doubled the amount of ligand necessary to attain saturation and about doubled the level of fluorescence enhancement obtained at saturation for both all-trans retinol and 9-AS. Although there was not a significant change in the Kd, the substitution increased the calculated number of binding sites (N) from approximately 2 to approximately 4 per polypeptide. The other Arg->Gln mutants did not significantly change the Kd or N. None of the mutations compromised the ability of the module to protect all-trans retinol from degradation. CONCLUSIONS: Our data suggest that the function of the conserved arginines in IRBP is fundamentally different from that of other retinoid-binding proteins. These residues do not appear to play a role in defining the specificity of the ligand-binding domain. Rather, Arg1005 appears to play a role in defining the capacity of the domain. Our data suggest that the binding site consists of a single hydrophobic cavity promiscuous for fatty acids and all-trans retinol.

Author(s): Ostwald P ; Park SS ; Toledano AY ; Roth S
Address: Department of Anesthesia and Critical Care, University of Chicago, IL 60637, USA.
Title: Adenosine receptor blockade and nitric oxide synthase inhibition in the retina: impact upon post-ischemic hyperemia and the electroretinogram.

Source: Vision Res (VISION RESEARCH) 1997 Dec; 37 (24): 3453-61 Journal Code: XEP
Additional Info: ENGLAND
Standard No: ISSN: 0042-6989
Language: ENGLISH
Abstract: We preformed this study to determine the effect on ocular blood flow and the electroretinogram of either nitric oxide synthase (NOS) inhibition, adenosine receptor blockade or the combination of both after 1 hr of ocular ischemia. Thirty-seven cats under general anesthesia were subjected to 1 hr of complete ischemia in one eye by raising the intraocular pressure above systolic blood pressure. The other eye in each animal served as a non-ischemic control. Arterial blood gas tension, systemic arterial pressure, body temperature, hematocrit, and anesthetic level were controlled in each experiment. Cats were divided into four groups. Group 1 received normal saline injections [intravenous (i.v.) and intravitreal], Group 2 adenosine receptor blockade (0.1 ml of 0.01 M 8-sulfophenyltheophylline intravitreal) and saline i.v., Group 3 NOS inhibition (30 mg/kg l-NG-nitroarginine-methyl-ester i.v.) and saline intravitreal, and Group 4 intravitreal adenosine receptor blockade and NOS inhibition i.v. A subset of Group 3 received l-arginine to investigate the reversibility of NOS inhibition, after the blood flow measurements were completed. Five minutes after the end of ischemia, blood flows in retina and choroid were measured using injections of radioactively labeled microspheres. Electroretinographic (ERG) studies were carried out before treatment, before ischemia, during ischemia, and 1, 2, 3, and 4 hr after ischemia ended. NOS inhibition significantly reduced basal blood flow in the choroid, and in the retina when combined with adenosine receptor blockade. Adenosine receptor blockade completely attenuated post-ischemic hyperemia in the retina, but retinal hyperemia reappeared when adenosine receptor blockade and NOS inhibition were combined. Adenosine receptor blockade had no effect on ERG recovery after ischemia. NOS inhibition led to a reduction of ERG a- and b-wave amplitudes in control eyes, that could be reversed by l-arginine. Nitric oxide (NO) appears to be a significant factor in the regulation of basal blood flow in the choroid. Adenosine appears to be a major mediator of retinal hyperemia after 60 min of ischemia. Since NOS inhibition appeared to have direct effects on ERG wave amplitudes, short-term ERG studies may be of limited use in assessing the role

of NO in postischemic recovery of the retina. Our observations correlate well with the emerging role of NO as a neurotransmitter in the retina.

Author(s): Goldstein IM ; Ostwald P ; Roth S
Address: Department of Anesthesia and Critical Care, University of Chicago, IL 60637, USA.
Title: **Nitric oxide: a review of its role in retinal function and disease.**
Source: Vision Res (VISION RESEARCH) 1996 Sep; 36 (18): 2979-94
Abstract: Nitric oxide synthase (NOS), the enzyme that catalyzes the formation of nitric oxide from L-arginine, exists in three major isoforms, neuronal, endothelial, and immunologic. Neuronal and endothelial isoforms are constitutively expressed, and require calcium for activation. Both of these isoforms can be induced (i.e., new protein synthesis occurs) under appropriate conditions. The immunologic isoform is not constitutively expressed, and requires induction usually by immunologic activation; calcium is not necessary for its activation. Neuronal and immunologic NOS have been detected in the retina. Neuronal NOS may be responsible for producing nitric oxide in photoreceptors and bipolar cells. Nitric oxide stimulates guanylate cyclase of photoreceptor rod cells and increases calcium channel currents. In the retina of cats, NOS inhibition impairs phototransduction as assessed by the electroretinogram. Inducible nitric oxide synthase, found in MŸller cells and in retinal pigment epithelium, may be involved in normal phagocytosis of the retinal outer segment, in infectious and ischemic processes, and in the pathogenesis of diabetic retinopathy. Nitric oxide contributes to basal tone in the retinal circulation. To date, findings are conflicting with respect to its role in retinal autoregulation. During glucose and oxygen deprivation, nitric oxide may increase blood flow and prevent platelet aggregation, but it may also mediate the toxic effects of excitatory amino acid release. This reactive, short-lived gas is involved in diverse processes within the retina, and its significance continues to be actively studied.

Author(s): Winderickx J ; Sanocki E ; Lindsey DT ; Teller DY ; Motulsky AG ; Deeb SS
Address: Department of Medicine, University of Washington, Seattle 98195.
Title: Defective colour vision associated with a missense mutation in the human green visual pigment gene.
Source: Nat Genet (NATURE GENETICS) 1992 Jul; 1 (4): 251-6

Journal Code: BRO
Additional Info: UNITED STATES
Standard No: ISSN: 1061-4036
Language: ENGLISH
Abstract: All red/green colour vision defects described so far have been associated with gross rearrangements within the red/green opsin gene array (Xq28). We now describe a male with severe deuteranomaly without such a rearrangement. A substitution of a highly conserved cysteine by arginine at position 203 in the green opsins presumably accounted for his colour vision defect. Surprisingly, this mutation was fairly common (2%) in the population but apparently was not always expressed. In analogy with nonexpression of some 5'green-red hybrid genes in persons with normal colour vision, we suggest that failure of manifestation occurs when the mutant gene is located at a distal (3') position among several green opsin genes. This mutation might also predispose to certain X-linked retinal dystrophies.

Author(s): Weitz CJ ; Miyake Y ; Shinzato K ; Montag E ; Zrenner E ; Went LN ; Nathans J
Address: Department of Molecular Biology, Johns Hopkins University School of Medicine, Baltimore 21205.
Title: Human tritanopia associated with two amino acid substitutions in the blue-sensitive opsin.
Source: Am J Hum Genet (AMERICAN JOURNAL OF HUMAN GENETICS) 1992 Mar; 50 (3): 498-507 Journal Code: 3IM
Additional Info: UNITED STATES
Standard No: ISSN: 0002-9297
Language: ENGLISH
Abstract: Tritanopia is an autosomal dominant genetic disorder of human vision characterized by a selective deficiency of blue spectral sensitivity. The defect is manifested within the retina and could be caused by a deficiency in function or numbers (or both) of blue-sensitive cone photoreceptors. We have used PCR, denaturing gradient gel electrophoresis, and DNA sequencing of amplified exons to detect in four of nine unrelated tritanopic subjects two different point mutations in the gene encoding the blue-sensitive opsin, each leading to an amino acid substitution. Segregation analysis within pedigrees and hybridization of oligonucleotides specific for each allele to DNA samples from control subjects support the hypothesis that these mutations cause tritanopia. These results complete the genetic evidence for the trichromatic theory of human color vision.

Author(s): Vannas-Sulonen K ; Simell O ; SipilS I
Address: Department of Ophthalmology, University of Helsinki, Finland.
Title: Gyrate atrophy of the choroid and retina. The ocular disease progresses in juvenile patients despite normal or near normal plasma ornithine concentration.
Source: Ophthalmology (OPHTHALMOLOGY) 1987 Nov; 94 (11): 1428-33 Journal Code: OI5
Additional Info: UNITED STATES
Standard No: ISSN: 0161-6420
Language: ENGLISH
Abstract: Hyperornithinemia disappeared in three children with Gyrate atrophy of the choroid and retina during a low-arginine diet for 3 to 4 1/2 years. Because of the young age of the patients, we had an exceptional opportunity to follow the progression of the disease during this period. Despite the excellent biochemical control, electroretinographic changes progressed in two patients, and the chorioretinal atrophy progressed steadily in all the patients throughout the diet. Dark adaptation and color vision remained stable. In these patients, the normo-ornithinemia has not been able to halt the progression of the chorioretinal degeneration.

Author(s): McInnes RR ; Arshinoff SA ; Bell L ; McCulloch C
Title: **Treatment of gyrate atrophy of the choroid and retina with low arginine diet.**
Source: Trans Am Ophthalmol Soc (TRANSACTIONS OF THE AMERICAN OPHTHALMOLOGICAL SOCIETY) 1980; 78: 226-42
Journal Code: W49
Additional Info: UNITED STATES
Standard No: ISSN: 0065-9533
Language: ENGLISH
Abstract: In gyrate atrophy the blood ornithine is grossly elevated, due to deficiency of ornithine ketoacid transaminase, which converts ornithine towards glutamic acid. Two patients with gyrate atrophy have been treated with a low arginine diet and their blood ornithine levels have been reduced to near normal. At this level hyperammonemia may result from overtreatment, but this can be quickly cleared by a small dose of arginine. There has also been some improvement in vision, but no clearing of the gyrate areas. Future care with this regimen seems possible and improvements in handling of these patients are likely.

Author(s): Kaiser-Kupfer MI ; de Monasterio F ; Valle D ; Walser M ; Brusilow S

Title: **Visual results of a long-term trial of a low-arginine diet in gyrate atrophy of choroid and retina.**
Source: Ophthalmology (OPHTHALMOLOGY) 1981 Apr; 88 (4): 307-10 Journal Code: OI5
Additional Info: UNITED STATES
Language: ENGLISH
Abstract: Visual function has been serially assessed in two gyrate atrophy patients who have had long-term reduction of plasma ornithine concentrations by a low-arginine diet. One patient demonstrated subjective and objective improvement after 15 months of treatment. In addition to improvements in dark adaptation thresholds, enlargement of visual fields, and a more normal electroretinogram, there was marked improvement in cone function as measured by color vision. There has been no change noted in the second patient. These results suggest that reduction of plasma ornithine may be beneficial in gyrate atrophy patients and that the high ornithine concentrations characteristic of this disorder play some role in the pathophysiology.

Author(s): Valle D ; Walser M ; Brusilow SW ; Kaiser-Kupfer M
Title: **Gyrate atrophy of the choroid and retina: amino acid metabolism and correction of hyperornithinemia with an arginine-deficient diet.**
Source: J Clin Invest (JOURNAL OF CLINICAL INVESTIGATION) 1980 Feb; 65 (2): 371-8 Journal Code: HS7
Abstract: Four patients with gyrate atrophy of the choroid and retina were studied, all of whom exhibited the hyperornithinemia characteristic of this disorder. Elevated plasma histidine and diminished plasma lysine and branched-chain amino acids were also noted. The renal clearances of these four amino acids were not sufficiently elevated to explain their low plasma levels. In one subject, an arginine-deficient diet led to progressive reduction in plasma ornithine from 13 times normal to the upper limits of normal, along with the disappearance of ornithinuria and lysinuria. Orally administered alpha-aminoisobutyric acid facilitated the fall in plasma ornithine by increasing renal losses of ornithine. It also increased the clearances of most other amino acids. When plasma ornithine approached normal (less than 200 microM), plasma lysine became normal, plasma arginine became subnormal, and renal clearances of basic amino acids decreased. Long-term (1.5 yr) maintenance with a diet containing 10-20 g of protein plus essential amino acids served to keep plasma ornithine at between 55-355 microM; chorioretinal degeneration did not progress and vision apparently

improved.

IMMUNOLOGY

Author: Albina, JE; Caldwell, MD; Henry, WL; & Mills, CD
Title: **Regulation of macrophage function by L-Arginine.**
Source: Journal of Experimental Medicine, 169 (1989) 1021-1029.

Author: Barbul, A; Fishel, RS et.al.
Title: **Intravenous alimentation with high arginine levels improves wound healing and immune function.**
Source: Journal of Surgical Research, 38 (1985) 228-334.

Author: Daly, J; Reynolds, J; et al.
Title: **Immune and metabolic effects of arginine in the surgical patient**.
Source: Annals of Surgery, 208 (1988) 512-523.