

Sunny James,

I checked out what information I could find on the liver and the use of arginine. Below are several medically published reports showing promise in the use of arginine and the liver and one report with a warning for people who are critically ill patients who suffer from hepatic failure. In the book entitled *Arginine Solution*, there is one report of increased nitric oxide production in cirrhosis may contribute to low blood pressure complication in advanced disease. However, they show several other medical reports showing nitric oxide is an important mediator of impaired oxygenation in patients with cirrhosis, arginine lowers tumor protein synthesis and tumor growth rate in liver cancer arginine alleviates cirrhosis of the liver, arginine helps to detoxify the liver and liver malfunction can occur as a result of arginine deficiency.

Basically I could only find two reasons not to take arginine and neither of those cases apply to you, and a host of reasons showing it is critical for the prevention and reversal of liver disease.

Lack of detrimental effects of nitric oxide inhibition in bile duct-ligated rats with hepatic encephalopathy.

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BACKGROUND: The pathogenetic mechanisms of hepatic encephalopathy (HE) are not fully understood. Vasodilatation induced by nitric oxide (NO) may be involved in the development of HE. There is no comprehensive data concerning the effects of NO inhibition on HE in chronic liver disease. **METHODS:** Male Sprague-Dawley rats weighing 240-270 g at the time of surgery were selected for experiments. Secondary biliary cirrhosis was induced by bile duct ligation (BDL). Counts of movements were compared between BDL rats and rats receiving a sham operation. In another series of experiments, BDL rats received either Nomega-nitro-L-arginine methyl ester (L-NAME, 25 mg kg⁻¹ day⁻¹ in tap water) or tap water (control) from the 36th to 42nd days after BDL. Besides motor activities, plasma levels of tumour necrosis factor (TNF)-alpha and nitrate/nitrite, liver biochemistry tests and haemodynamics were determined after treatment. **RESULTS:** Compared with the sham-operated rats, the total, ambulatory and vertical movements were significantly decreased in the BDL rats ($P \leq 0.001$). The L-NAME group had a significantly higher mean arterial pressure than that of the control group (119.0 +/- 2.5 mmHg vs. 97.3 +/- 2.8 mmHg, $P = 0.002$). However, the counts of motor activities, plasma levels of TNF-alpha and nitrate/nitrite, and serum biochemistry tests were not significantly different

between the L-NAME and control groups. CONCLUSIONS: Bile duct ligation may induce HE evidenced by a decrease in motor activities. However, chronic L-NAME administration did not have significantly detrimental or therapeutic effects on the severity of encephalopathy in BDL rats.

Direct evidence that induced nitric oxide production in hepatocytes prevents liver damage during lipopolysaccharide tolerance in rats.

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BACKGROUND: The role of nitric oxide (NO) in lipopolysaccharide (LPS) tolerance in the liver has been investigated in a number of previous studies, but it is still not clear whether NO is cytotoxic or cytoprotective. The aims of this study were to investigate whether low-dose LPS (LLPS)-induced hepatic production of NO is beneficial and to clarify the origins of cytoprotective NO-producing cells in the liver during LPS tolerance. **MATERIALS AND METHODS:** Male Wistar rats received saline or LLPS intraperitoneally (i.p.; 0.01-1000 microg/kg) followed by a high dose of LPS (HLPS, 5 mg/kg) at various time intervals (4-16 h). NG-nitro-L-arginine methyl ester (L-NAME) was used to investigate the effects of inhibition of NOS. 4,5-Diaminofluorescein (DAF-2) was used to identify NO-producing cells in isolated liver cells in vitro. At various time points (4-16 h) after saline or LLPS (1 microg/kg, i.p.) injection, hepatocytes and Kupffer cells were isolated, incubated in 7 microm DAF-2 diacetate, and perfused with Krebs solution. Illumination at 495 nm revealed DAF-fluorescence (515 nm) in isolated cells under confocal laser fluorescence microscopy. The NO production in hepatocytes and Kupffer cells was assessed by the number of labeled cells per 1000 cells or per 100 cells, respectively. **RESULTS:** Pretreatment with LLPS (0.1-100 microg/kg) resulted in a significant reduction (maximal at 8 h) of the HLPS-induced liver damage. L-NAME abolished the LLPS-induced protection. The NO production in hepatocytes was significantly increased and reached a maximum of 84% of all cells 8 h after LLPS administration. By contrast, the NO production in Kupffer cells remained constant at 95%, even following preinjection of LLPS. **CONCLUSION:** LLPS-induced NO in hepatocytes, but not in Kupffer cells, exhibits cytoprotective effects on HLPS-induced liver damage, suggesting that NO has a beneficial role in the induction of the early phase of LPS tolerance.

Effects of intravenous amino acid administration with Y-90 DOTA-Phe1-Tyr3-Octreotide (SMT487[OctreoTher] treatment.

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Y-90-DOTA-Phe1-Tyr3-Octreotide (90Y-SMT 487, OctreoTher) has shown potential for effectively treating patients with neuroendocrine tumors. The dose-limiting organ for this agent is the kidney. The purpose of this work is to assess the effectiveness of a commercially available amino acid solution on reducing renal uptake of 90Y-SMT 487 and determine the safety profile of this solution. Subjects with In-111 pentetreotide positive tumors and normal creatinine levels were treated with 3 cycles of 90Y-SMT 487, 120 mCi/cycle, at 6-9 week intervals. During each treatment two liters of an amino acid solution containing arginine and lysine (Aminosyn II 7%, Abbott Laboratories, Abbott Park, IL) were infused IV over 4 hours. Adverse events were recorded. To assess the effect of Aminosyn II on renal uptake of 90Y-SMT 487, a subgroup of subjects underwent bremsstrahlung imaging 24 hours following infusion. Kidney to liver (K/L) count density ratios were generated from the baseline In-111 pentetreotide images (performed without amino acid infusion) and the 90Y bremsstrahlung images. Follow-up creatinine levels were obtained. Thirty-seven subjects received a total of 89 90Y-SMT 487 treatments. The number of amino-acid infusions associated with one or more episodes of emesis was 53 (62%). During 13 (15%) of these infusions, the Aminosyn II rate had to be reduced because of severe nausea and vomiting. Symptomatic flushing occurred during 16 (18%) of the infusions. One subject experienced a near syncopal event shortly after completing the infusion. Creatinine levels remained normal in 34 of 36 subjects during a mean follow-up period of 9.8 months. Fourteen subjects underwent bremsstrahlung imaging following infusion of 90Y-SMT 487. Kidney uptake appeared to decrease with administration of the amino acid solution in 13 of 14 subjects. For the 28 individual kidneys, the mean percent decrease in the Kidney/Liver uptake ratio with the amino acid solution was found to be 32%. We conclude that 2 L of Aminosyn II 7% infused over 4 hours appears to notably reduce renal uptake of 90Y-SMT 487. Aminosyn is generally well tolerated, particularly at lower infusion rates with occasional moderate to severe nausea and vomiting at higher rates.

The urea cycle and related pathways in the liver of Walker-256 tumor-bearing rats.

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The urea cycle was evaluated in perfused livers isolated from cachectic tumor-bearing rats (Walker-256 tumor). Urea production in livers of tumor-bearing rats was decreased in the presence of the following substrates: alanine, alanine + ornithine, alanine + aspartate, ammonia, ammonia + lactate, ammonia + pyruvate and glutamine. Urea production from arginine was higher in livers of tumor-bearing rats. No difference was found with aspartate, aspartate + ammonia, citrulline, citrulline + aspartate and glutamine + aspartate. Ammonia consumption was smaller in livers from cachectic rats when the substance was infused together with lactate and pyruvate. Glucose production was smaller in the cachectic condition only when alanine was the gluconeogenic substrate. Blood urea was higher in tumor-bearing rats, suggesting higher rates of urea production. The availability of aspartate seems to be critical for urea synthesis in the liver of tumor-bearing rats, which is possibly unable to produce this amino acid in sufficient amounts from endogenous sources. The liver of tumor-bearing rats may have a different exogenous substrate supply of nitrogenous compounds. Arginine could be one of these compounds in addition to aspartate which seems to be essential for an efficient ureogenesis in tumor-bearing rats.

L-Arginine ameliorates oxidative stress in alloxan-induced experimental diabetes mellitus.

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Oxidative stress occurs in diabetic patients and experimental models of diabetes. The ability of l-arginine to ameliorate the oxidative stress and metabolic changes after treatment with alloxan was investigated in rats. Adult male rats were injected intraperitoneally with 100 mg kg⁻¹ of alloxan to produce experimental oxidative stress characteristic of diabetes mellitus. Hyperglycaemia and hypercholesterolaemia were observed in serum after 7 days of alloxan treatment. This was associated with a depression of glutathione (GSH) concentration as well as superoxide dismutase (SOD) and catalase (CAT) activities in the liver and brain. In addition, the thiobarbituric acid-reactive substances (TBARS) were significantly elevated, indicating increased lipid peroxidation and oxidative stress in the same tissues. Administration of 100 mg kg⁻¹ l-arginine for 7 days either before or after alloxan injection significantly ameliorated the oxidative stress evidenced by a lower TBARS and a higher level of the endogenous GSH concentration and SOD and CAT activities than alloxan-treated rats. These effects were paralleled by marked protection and partial prophylaxis against alloxan-induced hyperglycaemia and cholesterolaemia. Thus, these results showed that exogenously administered l-arginine might improve the clinical manifestation of diabetes mellitus and decrease the oxidative stress in the liver and brain. In addition, the study supports the beneficial effect of l-arginine, which might be attributed to its direct, NO-dependent antioxidant capacity and/or NO-independent pathways. Copyright 2004 John Wiley & Sons, Ltd.

High plasma arginine concentrations in critically ill patients suffering from hepatic failure.

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OBJECTIVE: In physiological conditions, the liver plays an important role in the regulation of plasma arginine concentrations by taking up large amounts of arginine from the hepatic circulation. When hepatic failure is present, arginine metabolism may be disturbed. Therefore, we hypothesized high arginine plasma concentrations in critically ill patients suffering from hepatic failure. **DESIGN:** We prospectively collected blood samples from a cross-section of intensive care unit patients. **SETTING:** Surgical intensive care unit of a Dutch university medical center. **SUBJECTS:** A total of 52 critically ill patients with clinical evidence of dysfunction of more than two organs were recruited. **MEASUREMENTS:** Plasma arginine concentrations were determined by HPLC. We identified correlations of arginine concentrations with organ failure scores and laboratory variables by univariate and multiple regression analyses. **RESULTS:** High plasma arginine concentrations were found in critically ill patients developing organ failure. Patients who were in the highest quartile of plasma arginine concentrations had significantly lower fibrinogen concentrations, higher lactic acid concentrations, and longer prothrombin time. Stepwise multiple regression analysis showed that concentrations of arginine were independently associated with the presence of hepatic failure ($P=0.03$) and renal failure ($P=0.048$). In addition, lactic acid proved to be an independent determinant of plasma arginine concentration ($P=0.014$). **CONCLUSIONS:** Critically ill patients who suffer from hepatic failure have elevated plasma arginine concentrations. Additional arginine in the treatment of these patients can be harmful, and therefore should not be used as a standard nutritional regimen until further evaluation.

Effects of tumor necrosis factor, endothelin and nitric oxide on hyperdynamic circulation of rats with acute and chronic portal hypertension.

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AIM: To evaluate the effect of tumor necrosis factor (TNF), endothelin (ET) and nitric oxide (NO) on hyperdynamic circulation (HC) of rats with acute and chronic portal hypertension (PHT). **METHODS:** Chronic portal hypertension was induced in Wistar rats by injection of carbon tetrachloride. After two weeks of cirrhosis formation, L-NMMA (25 mg/kg) was injected into one group of cirrhotic rats via femoral vein and the

experiment was begun immediately. Another group of cirrhotic rats was injected with anti-rat TNFalpha (300 mg/kg) via abdominal cavity twice within 48 h and the experiment was performed 24 h after the second injection. The blood concentrations of TNFalpha, ET-1 and NO in portal vein and the nitric oxide synthase (NOS) activity in hepatic tissue were determined pre-and post-injection of anti-rat TNFalpha or L-NMMA. Stroke volume (SV), cardiac output (CO), portal pressure (PP), superior mesenteric artery blood flow (SMA flow) and iliac artery blood flow (IAflow) were measured simultaneously. Acute portal hypertension was established in Wistar rats by partial portal-vein ligation (PVL). The parameters mentioned above were determined at 0.5 h, 24 h, 48 h, 72 h and 120 h after PVL. After the formation of stable PHT, the PVL rats were injected with anti-rat TNFalpha or L-NMMA according to different groups, the parameters mentioned above were also determined. RESULTS: In cirrhotic rats, the blood levels of TNFalpha, NO in portal vein and the liver NOS activity were significantly increased ($P < 0.05$) while the blood level of ET-1 was not statistically different ($P > 0.05$) from the control animals (477.67 \pm 83.81 pg/mL vs 48.87 \pm 32.79 pg/mL, 278.41 \pm 20.11 micromol/L vs 113.28 \pm 14.51 micromol/L, 1.81 \pm 0.06 u/mg.prot vs 0.87 \pm 0.03 u/mg.prot and 14.33 \pm 4.42 pg/mL vs 8.72 \pm 0.79 pg/mL, respectively). After injection of anti-rat TNFalpha, the blood level of TNFalpha was lower than that in controls (15.17 \pm 18.79 pg/mL vs 48.87 \pm 32.79 pg/mL). The blood level of NO and the liver NOS activity were significantly decreased, but still higher than those of the controls. The blood level of ET-1 was not significantly changed. PP, SV, CO, SMAflow and IAflow were ameliorated. After injection of L-NMMA, the blood level of NO and the liver NOS activity were recovered to those of the controls. PP and CO were also recovered to those of the controls. SV, SMAflow and IAflow were ameliorated. In PVL rats, the blood levels of TNFalpha, NO in portal vein and the liver NOS activity were gradually increased and reached the highest levels at 48 h after PVL. The blood level of ET-1 among different staged animals was not significantly different from the control animals. PP among different staged animals (2.4 \pm 0.18 kPa at 0.5 h, 1.56 \pm 0.08 kPa at 24 h, 1.74 \pm 0.1 kPa at 48 h, 2.38 \pm 0.05 kPa at 72 h, 2.39 \pm 0.16 kPa at 120 h) was significantly higher than that in controls (0.9 \pm 0.16 kPa). After injection of anti-rat TNFalpha in 72 h PVL rats, the blood level of TNFalpha was lower than that in controls (14 \pm 14 pg/mL vs 48.87 \pm 32.79 pg/mL). The blood level of NO and the liver NOS activity were significantly decreased, but still higher than those of the controls. The blood level of ET-1 was not significantly changed. PP was decreased from 2.38 \pm 0.05 kPa to 1.68 \pm 0.12 kPa, but significantly higher than that in controls. SV, CO, SMAflow and IAflow were ameliorated. After injection of L-NMMA in 72 h PVL rats, the blood level of NO and the liver NOS activity were recovered to those of the controls. PP, SV, CO, SMAflow and IAflow were also recovered to those of the controls. CONCLUSION: NO plays a critical role in the development and maintenance of HC in acute PHT and is a key factor for maintenance of HC in chronic PHT. TNFalpha may not participate in the hemodynamic changes of HC directly, while play an indirect role by inducing the production of NO through activating NOS. No evidence that circulating ET-1 plays a role in both models of portal hypertension has been found.

Effects of L-arginine-enriched total enteral nutrition on body weight gain, tumor growth, and in vivo concentrations of blood and tissue metabolites

in rats inoculated with Walker tumor in the kidney.

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OBJECTIVE: We evaluated the effects of l-arginine-enriched total enteral nutrition (LATEN) on tumor-free and right kidney tumor-bearing rats through the determination of in vivo concentrations of metabolites to better understand intermediary metabolism in this model. **METHODS:** Rats were individually housed in wire cages within a controlled environment (25 degrees C and 50% relative humidity) and exposed to a 12-h light-and-dark cycle. Rats comprised the following groups: tumor-free on enteral nutrition plus l-amino acid (n = 8); tumor-free on enteral nutrition plus l-arginine (n = 8); tumor bearing on enteral nutrition plus l-amino acids (n = 8); and tumor bearing on enteral nutrition plus l-arginine (n = 8). Rats had their right kidneys inoculated with saline or tumor cells and were subjected to laparotomy or gastrostomy on day 1 and received chow diet for the next 2 days. Gastrostomy with enteral nutrition was performed on days 3 to 9. On day 9, body weight gain, tumor growth as volume, in vivo blood (microM/mL), and tissue (microM/g) metabolite concentrations were determined. The Mann-Whitney U test was used to test significance. **RESULTS:** LATEN in tumor-free rats decreased liver (0.25 +/- 0.03 versus 0.13 +/- 0.03 micromol/g, P < 0.05) and right kidney (0.13 +/- 0.1 versus 0.04 +/- 0.00 micromol/g, P < 0.05) ketone body concentrations. LATEN in tumor-bearing rats decreased blood pyruvate (0.17 +/- 0.01 versus 0.10 +/- 0.008 microM/mL, P < 0.005), lactate (5.2 +/- 0.3 versus 2.9 +/- 0.28 microM/mL, P < 0.01), and glucose (6.4 +/- 0.8 versus 3.7 +/- 0.5 microM/mL, P < 0.05). Glucose concentrations decreased in liver (13.9 +/- 2.0 versus 4.89 +/- 0.6 microM/g, P < 0.005) and tumor (3.5 +/- 0.8 versus 1.41 +/- 0.3 microM/g, P < 0.05). There were no changes in body weight gain (21 +/- 2.0 versus 30.3 +/- 3.6 g) or tumor growth (1.53 +/- 0.1 versus 1.26 +/- 0.01 cm(3)). **CONCLUSIONS:** LATEN decreased ketone body concentrations in liver and kidney in tumor-free rats, possibly due to lower ketogenesis and decreased kidney uptake. In tumor-bearing rats, LATEN decreased lacticemia and glycemia and pyruvate blood concentrations. LATEN also reduced liver and tumor glucose concentrations in tumor-bearing animals. The possibility of LATEN-induced insulin and insulin-like growth factor-1 liberation signaling these changes is discussed.

Hope this helps,

Dr Harry