A breakthrough in recuperation for cats and dogs.

Why and how to feed the gut?

The 4 essential recuperation nutrients: Glutamine, Arginine, Omega 6/3 fatty acids and Taurine

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Recuperation

Why and how to feed the gut ?

Cats and dogs can undergo significant metabolic changes when recovering from a serious illness, injury or surgery. During these stressful conditions the body is challenged to maintain strong natural defenses and spare lean body mass, which makes it is even more important to feed the right food. Cats and dogs need extra nutrients, in an appetizing form, to encourage the recovery or recuperation process.

Why we need to feed the gut and prevent starving ?

Researchers have good documentation on how the dog's body organs and biochemistry are disrupted by various lengths of time of starvation. If the dog is healthy to begin with, and no medical problems exist that, of course, would compound the starving dog's medical status, a predictable sequence of adaptations take place. The dog's biochemical functions shift into survival mode within twenty-four hours with no nutritional intake. The highest priority of the dog's metabolic processes becomes the necessity to keep the blood glucose concentration at a normal level. If the blood glucose ("blood sugar") level drops too low for any reason, the brain, heart, muscles and kidney function shuts down rapidly and death comes quickly. So, when the dog has no opportunity to eat, the survival mode's first concern is to mobilize stored glucose from liver and muscle reserves by changing the biochemical processes to different chemical pathways that make glucose readily available.

After about two days without food the liver reserves of glycogen (glucose) are depleted. So in order to keep the blood level of glucose in the normal range, new chemical pathways open, called gluconeogenesis, where the liver and kidneys create molecules from complicated biochemical reactions so that fats and proteins are extracted from adipose tissue and muscle. As the glucose reserves are tapped and diminished, chemical reactions kick in to create glucose internally from those protein and fat reserves. Energy to run the body's machinery (muscle, brain, kidney, heart and other organ functions require energy to fuel their activities) is now fueled less by glucose and more by fatty acid extracted from fat reserves.

On the third day of food deprivation the dog's metabolism (metabolism refers to all the chemical reactions going on to maintain life) slows down. This lower, or slowed metabolic rate continues as long as no food is consumed. The lowered metabolism is a survival mechanism to decrease the utilization of body fat and muscle for energy. Lowered blood sugar levels changes insulin secretion by the pancreas, which in turn lowers thyroid hormone levels; and it's the thyroid gland function that ultimately dictates the metabolic rate.

During starvation the liver releases chemicals called ketones into the blood stream; ketones are then used as a source of energy for the dog's body cells. By creating ketones and fatty acids to be used as energy sources, the dog's body conserves what little glucose is circulating so that glucose-dependent red blood cells and important kidney tissues can continue to access glucose. Interestingly, red blood cells and kidney tubule cells cannot utilize anything other than glucose for cell energy needs.

After five days of starvation fat becomes the main source of energy.

A prolonged lack of food does not "shrink the stomach" but it does make the stomach much more sensitive to stretch receptor nerve impulses. The dog may feel as if full when the stomach has only a small quantity of food in the stomach. The increased sensitivity to gastric expansion will dissipate over 3 to 7 days.

The food being fed to the starved pet should have adequate mineral composition especially for phosphorous, potassium and magnesium. A broad-spectrum vitamin and mineral supplement is important to include at each meal. Some evidence supports the addition of the amino acid glutamine to the recovery of the pet. Omega 3 and 6 Fatty Acid supplements are beneficial to the recovering animal. The amino acid Arginine should be plentiful in the recovery meal.

Critically ill patients, especially cats, are in a very unstable and dynamic phase of change. The effect of starvation is different and more severe in stressed animals compared to normal pets, and malnutrition can occur within a number of days. A number of specific nutrients have properties that may be beneficial in the nutritional management of critical care patients, including glutamine, arginine, branch-chain amino acids, B vitamins, and zinc. Cats in a "critical" state are by their very nature unstable and in a dynamic state of change. Once immediate life-threatening problems such as hemorrhage, shock, and/or other organ failures have been stabilized, the provision of nutritional support is essential for a rapid and successful recovery.

It has been estimated that up to 50% of hospitalized small animal patients are malnourished (Chandler et al. 1992). Cats that have suffered a traumatic incident or debilitating illness enter a stressed or hypermetabolic phase in which

tissue proteins are catabolized to provide building blocks for lifesaving functions such as antibody production, wound healing, and gluconeogenesis for maintenance of energy levels. In critically ill cats,which will not or cannot eat to replenish energy demands, the onset of malnutrition occurs within three to five days. Providing nutritional support to these patients can be very rewarding with numerous well-established benefits. The therapeutic benefits of nutritional support in critically ill cats are well established, and include:

- Decreased morbidity and mortality
- Improved tolerance to invasive procedures
- Shorter hospitalization periods
- Decreased incidence of infections
- Earlier ambulation
- Rapid wound healing
- Fewer complications

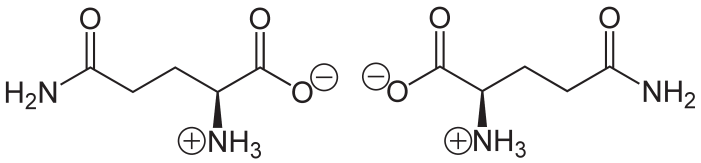
Enteral feeding is considered more physiologically sound than intravenous feeding, as it maintains the health of the gastrointestinal tract. The intact intestinal mucosa acts as an important barrier to bacteria, and it is therefore important to maintain the health of the gastrointestinal lining by supplying nutrients enterally. When the gut is starved, bacteria can translocate from the intestine into the circulation, leading to sepsis. Therefore, even patients receiving parenteral nutritional support may benefit from enteral feeding.

The 4 essential recuperation nutrients:
Glutamine, Arginine, Omega 6/3 fatty acids and Taurine.

There is evidence enough to accept the same effects on animals as found in humans.
Of course continous scientific research in pets will be of value.

1. Glutamine

Glutamine is not recognized as an essential amino acid but may become conditionally essential in certain situations as gastrointestinal disorders. The role of glutamine as an important and major substrate in rapidly dividing cells such as those of the gastrointestinal tract and the immune system (lymphocytes, macrophages, and thymocytes) is well known. Glutamine is responsible for maintaining the IgAsecreting cells of the gut mucosa and an adequate supply is, therefore, required to ensure the integrity of the intestinal mucosal barrier. A deficiency in glutamine results in small intestinal villus atrophy and a compromise in the mucosal barrier, which may ultimately lead to bacterial translocation and sepsis. Brush border enzymes, which aid in digestion,down-regulate their own activity, making the digestive process much less efficient. Also during stress or trauma, the synthesis of glutamine is not able to match the increase in uptake and metabolism by the gastrointestinal tract. Therefore, glutamine has been described as a "conditionally essential amino acid" (Lacey and Wilmore 1990, Mobrahan 1992). This increased demand and concurrent poor supply in trauma patients may result in a compromise of the gut mucosal barrier, resulting in subsequent bacterial translocation and systemic infection (Souba et al. 1990). Although specific recommendations for levels of this amino acid in critical patients are lacking, the benefits of supplementation have been demonstrated in multiple studies.



Glutamine zwitterionic forms at neutral pH: L-glutamine (left) and D-glutamine (right)

Glutamine plays a role in a variety of biochemical functions including:

- Protein synthesis, as any other amino acid.
- It is a precursor of puric and pyrimidic bases.
- It regulates some hepatic syntheses.
- Regulation of acid-base balance in the kidney by producing ammonium.
- Cellular energy, as a source, next to glucose.
- Nitrogen donation for many anabolic processes.
- Carbon donation, as a source, refilling the citric acid cycle.
- Nontoxic transporter of ammonia in the blood circulation.
- It participates in detoxification processes.

In catabolic states of injury and illness, glutamine becomes conditionally-essential (requiring intake from food or supplements). Glutamine has been studied extensively over the past 10–15 years in humans and has been shown to be useful in treatment of serious illnesses, injury, trauma, burns, and treatment-related side-effects of cancer as well as in wound healing for postoperative patients.[1]
Glutamine might help gut function, the immune system, and other essential processes in the body, especially in times of stress. It is also important for providing "fuel" (nitrogen and carbon) to many different cells in the body. Glutamine is needed to make other chemicals in the body such as other amino acids and glucose (sugar).

After surgery or traumatic injury, nitrogen is necessary to repair the wounds and keep the vital organs functioning. About one third of this nitrogen comes from glutamine.

Aiding recovery after surgery
It is also known that glutamine has various effects in reducing healing time after operations. Hospital-stay times after abdominal surgery can be reduced by providing parenteral nutrition regimes containing high amounts of glutamine to patients. Clinical trials have revealed that patients on supplementation regimes containing glutamine have improved nitrogen balances, generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes, and improved lymphocyte recovery and intestinal permeability (in postoperative patients), in comparison to those that had no glutamine within their dietary regime, all without any side-effects.[2]

1. Glutamine, University of Maryland Medical Center, http://www.umm.edu/altmed/articles/glutamine-000307.htm, retrieved 2009-09-06.

2. Morlion, Bart J.; Stehle, Peter; Wachtler, Paul; Siedhoff, Hans-P.; Köller, Manfred; König, Wolfgang; Fürst, Peter; Puchstein, Christoph (1998), "Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study", Ann. Surg. 227 (2): 302–8, doi:10.1097/00000658-199802000-00022, PMC 1191250, PMID 9488531

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Session III: Physiological Aspects of Glutamine Metabolism II—Discussion Summary[1]

Marc Rhoads

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Dr. Rhoads. Before opening the general discussion, I have been asked to review our laboratory's studies on the potential role of glutamine in the therapy of diarrheal disease.

Diarrheal disease kills more infants and children worldwide than any other condition except respiratory infections. That is why I became interested in glutamine. Dr. Lobley raised the question whether glutamine helps in diarrheal disease, and the answer is "yes" and "no." We have studied two disease models, piglet *rotavirus* infection, and piglet and calf *cryptosporidiosis*. My first investigations of glutamine had to do with super oral rehydration. Oral rehydration saves lives, but only 90% of infants can be rehydrated orally. If an infant resides in a developing country, there may be insufficient resources to provide intravenous fluids, which is one of the reasons why ~2.5 million children die annually of diarrheal disease.

Thus the concept was developed that adding amino acids to glucose in an oral rehydration solution (ORS)[2] should maximize sodium absorption. "Super ORS" may be more efficacious than standard ORS in human cholera, as was shown for L-alanine + glucose ORS in a double-blind WHO-funded trial in patients with cholera and enterotoxigenic *Escherichia coli* diarrhea (Patra et al. 1989). A problem is that cooked rice plus ORS, or rice-based ORS, may be equally effective and cheaper (Santosham et al. 1990). We have also found that not all amino acids are "created equal." Most of the studies investigated glycine, an amino acid that is not cotransported with Na^+ in the piglet intestine. We previously compared a number of amino acids in terms of their effects on net sodium flux in the piglet jejunum. When we studied glutamine, phenylalanine, alanine, proline, leucine and asparagine, the only ones that stimulated a substantial amount of sodium absorption were glutamine, phenylalanine and alanine. Phenylalanine was dismissed as an ORS additive because it could be toxic to the neonatal brain and children with phenylketonuria, and we focused on glutamine and alanine. Glutamine and glucose were equally effective, and they had *additive* effects on sodium absorption across the jejunum and ileum. This observation of additivity applied to the damaged intestine during piglet rotavirus infection. Even in severely infected tissues, there was an additive response to glucose plus glutamine, or glucose plus alanine. In another model, cryptosporidiosis of piglets and calves, glutamine was additive to glucose in enhancing Na^+ absorption in the intestine (Argenzio et al. 1994).

Additivity in stimulating absorption was attributable to the presence of separate brush border amino acid- and glucose-coupled sodium cotransporters, and also because glutamine stimulated electroneutral sodium chloride absorption. In human infants, glutamine plus glucose oral rehydration was investigated in studies funded by the WHO in India and Brazil. These studies investigated infants with mild diarrhea. Children often have diarrhea caused by a variety of pathogens, viruses in particular. Ribeiro et al. (1994) studied infants with mild dehydration. Their body weights, on admission compared with discharge, differed by only 2–3%. Additionally, the "Super ORS" given was hyperosmolar (>380 mOsm). Recently a number of investigations have shown that hypoosmolar oral rehydration is better than isoosmolar ORS. Thus the studies of hypertonic "Super ORS" in my opinion were inconclusive and should be repeated.

The other focus of our studies was whether glutamine would promote intestinal repair in piglet rotavirus infection. To summarize our studies, glutamine-supplemented ORS did not enhance repair (Rhoads et al. 1996). We have just completed another study in calf cryptosporidiosis in which supplementation with glutamine did not enhance the rate of recovery, although bovine serum concentrate was efficacious (Rhoads et al., in press). All of our studies looked at the duration and severity of diarrhea in well-nourished animals. One may ask whether glutamine would be more beneficial in poorly nourished subjects.

An important effect of glutamine in intestinal cells is that it stimulates mitogen-activated protein kinases (MAPK) by a metabolism-dependent but Raf-independent mechanism (Rhoads et al. 2000). This activation of MAPK is inhibited by cyclic AMP. Glutamine additionally affects a stress-activated protein kinase pathway, the c-Jun kinase pathway, in two different ways. If the cells are glutamine-starved, there is a progressive activation of Jun nuclear kinase (JNK) that depends on the duration of starvation, resulting in apoptosis, as has been shown by Papaconstantinou et al. (1998). But if the cells are starved for a short period of time and then glutamine is applied, JNK and the extracellular signal-regulated kinases (ERK)-1 and -2 are activated, and the cells undergo mitogenesis. A related finding was that epidermal growth factor, when

[1] Presented at the International Symposium on Glutamine, October 2–3, 2000, Sonesta Beach, Bermuda. The symposium was sponsored by Ajinomoto USA, Incorporated. The proceedings are published as a supplement to *The Journal of Nutrition*. Editors for the symposium publication were Douglas W. Wilmore, the Department of Surgery, Brigham and Women's Hospital, Harvard Medical School and John L. Rombeau, the Department of Surgery, the University of Pennsylvania School of Medicine.

[2] Abbreviations used: ERK, extracellular signal-regulated kinase; JNK, Jun nuclear kinase; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; NEC, necrotizing enterocolitis; ORS, oral rehydration solution; TPN, total parenteral nutrition.

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given to the cultured intestinal cell line IEC-6, stimulates thymidine incorporation twofold more when glutamine is present compared with when glutamine is absent.

Recently, we looked for evidence that glutamine levels might be relevant to pediatric intestinal disease. We investigated glutamine and arginine levels in newborn premature infants weighing <1800 g (Becker et al. 2000). It was a follow-up to two other studies (Dallas et al. 1998, Lacey et al. 1996) that showed better outcomes in premature children receiving glutamine supplementation. In a third related study by Zamora et al. (1997), infants with necrotizing enterocolitis (NEC) had lower serum levels of arginine, but not glutamine at the time of onset of NEC. In our study, we immediately stored serum from every infant that was premature and had each sample analyzed by HPLC by Dr. Guoyao Wu at Texas A&M University. We found that NEC occurred on mean day of life 14. This is the time at which the infants were just beginning to reach full enteral feeding. Before this, they were receiving primarily total parenteral nutrition (TPN). There were 16 infants who developed NEC and 35 age-matched normal premature infants. At ~10 d before the infants developed NEC, serum levels of specific amino acids, especially glutamine and arginine, began to fall below the levels of those who did not develop NEC (Becker et al. 2000).

NEC was demonstrated on the abdominal flat plate X-ray, which showed intramural air (air within the wall of bowel) or pneumatosis coli. Also, physical findings indicated that the children were sick. The control (no NEC) infants had a progressive increase in arginine and glutamine concentrations as they grew older. Median values of serum glutamine were 37–57% lower in NEC infants on d 7, 14 and 21, compared with controls ($P < 0.05$). On d 7 and 14, median values of arginine, alanine, lysine, ornithine and threonine were also decreased 36–67% ($P < 0.05$) in NEC infants compared with controls (Becker et al. 2000).

The results were not fully explainable on the basis of intake. Arginine (Arg) was especially interesting because Arg intake was actually twofold higher in the children that developed NEC because of the higher concentration of Arg in TPN than in formula. Because the children that developed NEC were receiving less enteral feeding, they took in much less glutamine compared with control infants. All of the children had a low intake of glutamine because there was no glutamine in the TPN (Becker et al. 2000). Our study raises the question whether low levels of serum glutamine or arginine could predispose to NEC.

I will open the session at this point for questions. Dr. Lobley, when you discussed movement of the glutamine nitrogen—what is the significance of more glutamine nitrogen going to methionine than to phenylalanine?

Dr. Lobley. It's a preferred substrate as the oxo-acid for methionine, rather than that for phenylalanine. In the liver, we showed a very clear differential among glutamine and phenylalanine and methionine enrichment, with the glutamate being much higher. For the plasma proteins, where we had a lower enrichment level simply because they have a much lower fractional synthesis rate, we found that the glutamate was about the same as the methionine. So it's a bit marginal as to whether it is coming from glutamate, and it was almost 100% transferred. I would often obtain equilibrium within the 6 h, which I find a bit suspicious. I hypothesize that it was transferred directly from glutamine, and did not go through glutamate.

Dr. Wernerman. We have learned today that there is still much to learn about the physiology of glutamine. We have seen studies in which glutamine has and has not produced favorable effects. It strikes me that there are very few studies in the literature in which glutamine has a negative effect. Now this means that if these positive results come by chance, there should be as many negative results by chance. On the other hand, if we do not understand physiology, perhaps experimental design (e.g., insufficient numbers of subjects) in a lot of studies showing no results is the major problem.

Dr. John Alverdy. Just as a follow-up to that comment, when we look at infection in humans, we think of it as occurring when the number or the virulence of a bacteria is balanced against the susceptibility or the resistance of the host. For example, opportunistic infections, infections that we create, are the worst infections in the hospital, certainly not the diarrheal infections resulting from contaminated food. It really is a unique set of circumstances in which the patients have lost lean body mass, or perhaps intracellular glutamine, and "we" have recolonized these patients with the most virulent hospital organisms. Those are the circumstances in which one might see the greatest benefit of glutamine, which is where you see some depletion in either intracellular or extracellular stores, and you see unique organisms colonizing the host. A "spritz," an infusion that evokes inflammation of lipopolysaccharides (LPS) and has a very short half-life in the blood, is not the same as a patient whose lungs are filled with gram-negative bacteria and who is on inadequate intravenous support. We went down this road 10 years ago where antiendotoxin antibodies were proposed as a magic bullet to treat these "end-stage" patients.

I believe the negative studies may belie the true effect that we are looking for, which is who are the most appropriate patients to target. They may be patients in whom there is unique susceptibility, and a pathogen that is not the meningitis pathogen, or the pathogens of pigs that produce diarrheal disease. The most feared pathogens may be the hospital pathogens.

Dr. Lobley. Dr. Wernerman said in the laws of chance you would expect some results to go negative, as well as positive. I do not totally agree with that. If your experiments are good enough, then you really should get a null effect, or you should get an effect, although that effect may be negative.

I agree with the comment of Dr. Alverdy, but to some extent I think it depends on where ones research is directed. I'm trying to understand whether there is a role for amino acids in challenge situations. To do that, I need a challenge situation that I can control. That's why we have gone for continuous infusion of LPS, rather than a single injection, because it gives us longer to investigate. It means that we are looking at a stable system. I'm not in a clinical situation. The other thing is I was forced by a home office inspector to start with well-fed sheep. We can actually study these animals under good conditions. It may well be that one of the experiments we will do in the future is to investigate animals under stressed conditions, when they have a low lean body mass. We may then find differential responses.

Dr. Alverdy. There has been a lot of interest in the United States about why some college dormitory students develop fatal meningitis, and what is unique about these students when everybody in the dormitory is exposed. Work is showing that not only are they exposed, but they actually may be immunologically weakened, because they have had long days of sleep deprivation and a lot of alcohol use.

And so again, under the paradigm of infection, where there must be unique host susceptibility and then there must be an unusual exposure to a pathogen that is both virulent and high in number, it seems to me that giving glutamine may help. When there is glutamine sufficiency in the animal, introduc-

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ing an organism that may or may not kill the animal and determining whether glutamine supplementation will change the course may not yield interpretable results. In a WHO trial, where you do not know what the organism is that is causing the diarrhea, looking at the effects of glutamine may not be the best study design, but it is certainly worth trying.

Participant. I want to make a comment about study design with regard to enteral glutamine administration. Adibi and Matthews, and others showed many years ago that a significant proportion of enteral protein digestion products are taken up in the form of di- and tripeptides. These substrates are transported by PEPT1, which is a molecule that transports the small peptides along a hydrogen-dependent gradient. In fasting humans and certain catabolic animal models, L-amino acid transport is impaired, whereas small peptide transport mediated by PEPT1 is maintained. In our studies of enteral glutamine supplementation, perhaps we should do comparative studies with a variety of glutamine peptides such as those Dr. Fürst and others have synthesized, that are now available for use. Additionally, we need to realize that enteral glutamine does not necessarily always mean L-glutamine administration. Perhaps peptide forms of enteral glutamine may be more efficacious.

I want to ask Dr. Häussinger to comment with regard to the cell swelling concept in cell lines. Apparently, there are no in vivo data in humans. Glutamate, I think, also can be transported by a sodium-dependent pathway, is this correct?

Dr. Häussinger. It's a very restricted sodium-dependent pathway in the liver, localized at the cannalicular membrane. So it's not clinically relevant.

Participant. Other amino acids can be transferred with sodium. Is this a swelling process, a sodium-dependent process or is there something unique about the effect of glutamine?

Dr. Häussinger. The hydration state of a cell in general is determined by the osmotic state that exists. And this osmotic state can be modified by all transport systems in the plasma membrane. This also means when a potassium channel is opened, potassium goes out of the cell and it shrinks. This is a mechanism of how oxygen radicals act by simply opening a potassium channel.

There are varied mechanisms by which cellular hydration is altered. There are many amino acids that are transported in a sodium-dependent way, and most of them induce cell swelling. As I hypothesized years ago, among the amino acids, glutamine is one of the "best swellers!"

Moreover, in contrast to transport systems like system A which has a lot of substrates, the N system only has one major substrate and this is glutamine. So it can be additive, and this was the reason why I emphasized sodium in my talk. I think this is one of the major reasons that glutamine is of interest.

Dr. Bode. If the activity of all of the known transport systems is measured in isolated hepatocytes, system N is by far the most active. There is a lot of flux through this carrier. I think one of the reasons that glutamine is such a good sweller is that it is transported very rapidly into the hepatocyte.

I'm not certain about the other tissues. In human cells, the ATB0 carrier is incredibly active. So this too may play a role. It may not just be system N.

Participant. With regard to the protein or the mRNA expression of system N in the membrane, is it regulated by the degree of swelling or shrinkage?

Dr. Häussinger. It is regulated by this mechanism as shown by Drs. Bode and Kilberg.

Dr. Bode. Actually, when swelling is induced artificially and plasma membrane vesicles are isolated, we found no evidence of additional carriers in the membrane. We believe that the swelling-induced activation in the carrier has to do more with post-translational modifications, or other driving forces within the cell that modulate its activity. In the kidney, there is evidence of withdrawal and reinsertion of different transporters. I believe they are ionic and not amino acid transporters. Thus there is precedent for osmotic regulation of protein trafficking. Dr. Häussinger pointed out that with the bile cannalicular carrier, this occurs as well. There is no evidence for additional system N insertion in response to cell swelling in the plasma membrane.

Dr. Häussinger. If you induce swelling in a cell, it swells to a certain point, and then you activate a regulatory potassium efflux, which tends to hyperpolarize the cell membrane; this energizes other transporters.

Participant. We investigated system N activation by glutamine. It's an autoregulatory loop that actually stimulates itself. If the extracellular potassium concentration is increased, the activation of system N is inhibited. This suggests a potentially major role for many of the ionic transporters and their interplay with amino acid transporters in regulating cell swelling induced glutamine flux. The picture is quite complicated.

Dr. Rhoads. The activation of MAP kinases does not always do the same thing to the cell. There are MAP kinases in the hepatocytes that are associated with changes in protein synthesis, transporters and proliferation. However, other amino acids, such as alanine, have major intracellular osmotic but not mitogenic effects in enterocytes. It may be that osmotic swelling of the intestinal cells activates MAP kinases without proliferation.

Dr. Häussinger. In the liver, alanine is a poor sweller.

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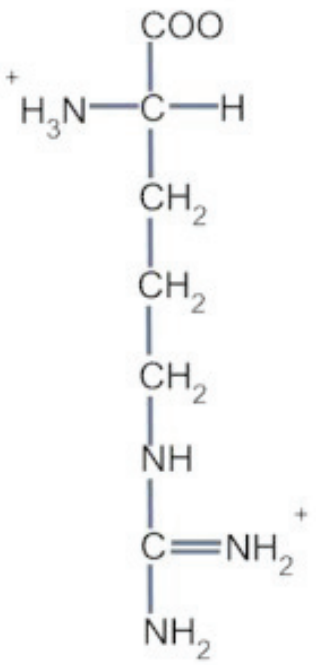
2. L-arginine

L-arginine is a chemical building block called “an amino acid.” It is obtained from the diet and is necessary for the body to make proteins. L-arginine is found in red meat, poultry, fish, and dairy products. Arginine is an essential amino acid in cats and dogs and has been shown to enhance cellular immunity, wound healing, and nitrogen balance (Barbul 1986). There are no specific indications for this amino acid in traumatized or stressed cats. However, as requirements may be increased in critically ill patients, a certain level of arginine supplementation is recommended in diets intended for these patients to support normal growth. Improving recovery after surgery by taking L-arginine with ribonucleic acid (RNA) and eicosapentaenoic acid (EPA) before surgery or afterwards seems to help reduce the recovery time, reduce the number of infections, and improve wound healing after surgery.



Arginine: an essential amino acid for injured rats.
Seifter E, Rettura G, Barbul A, Levenson SM.

Abstract

The influence of arginine supplements on growth and healing of skin incisional wounds was studied in rats fed either a chemically defined diet lacking arginine or a laboratory chow containing 1.8% arginine. Rats fed the arginine-free diet grew more poorly than did arginine-supplemented rats (1.8 vs. 7.0 gm/day) in the preoperative period. After operation arginine-deficient animals grew very poorly (1 gm/day), while arginine-supplemented rats gained 4.3 gm/day. Arginine-deficient animals showed impaired wound healing, as judged by the breaking strengths of their incisions 10 days after wounding (228 vs. 293 gm for the arginine-supplemented rats). Arginine-deficient rats also showed decreased collagen deposition in a specific wound site, as indicated by the decreased content in hydroxyproline in sponge granulomas (2.5 vs. 4.2 mg/100 mg. of sponge for the arginine-supplemented rats). In rats fed commercial chow, 1% arginine decreased the postoperative weight loss associated with injury (0.7 vs. 5.2 gm) in one experiment and improved wound strength in two experiments (312 vs. 188 gm in one experiment and 309 vs. 246 gm in another). Arginine also increased hydroxyproline deposition in a specific wound area (5.5 vs. 4.1 mg in one experiment and 3.1 vs. 1.9 mg. in another). It is concluded that arginine has two roles in wounded animals. It is essential for the synthesis of the increased amounts of reparative collagen required for wound healing, and it decreases some of the negative aspects of the metabolic responses to injury. These are thought to be associated with an arginine-induced growth hormone release.

Effects of L-Arginine and L-nitro-arginine methyl ester on recovery of neonatal lamb hearts after cold ischemia: Evidence for an important role of endothelial production of nitric oxide.

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Abstract

Myocardial ischemia and reperfusion results in both ventricular and endothelial dysfunction. We have found that the endothelial defect is a reduced vasodilator response to an intraarterial infusion of acetylcholine that is likely due to reduced nitric oxide release, and we have hypothesized that reduced endothelial nitric oxide production contributes to postischemic cardiac dysfunction. However, others report that nitric oxide is deleterious after ischemia. We therefore examined the effects of infusions of L -arginine (3 mmol/L), a precursor of nitric oxide, D-arginine (3 mmol/L), an inactive stereoisomer of L-Arginine, L -nitro-arginine methyl ester (1 mmol/L); a competitive inhibitor of nitric oxide synthase, and L-nitro-arginine methyl ester (1 mmol/L) plus L-Arginine (3 mmol/L) versus controls in isolated blood-perfused neonatal lamb hearts having 2 hours of cold cardioplegic ischemia. L -nitro-arginine methyl ester was given before reperfusion, and L -arginine and D-arginine were infused for the first 20 minutes of postischemic reperfusion. At 30 minutes of reperfusion, by comparison with the control group, the L -arginine group showed significantly better recovery ($p < 0.05$) of left ventricular systolic function (maximum developed pressure, developed pressure at V10 [balloon volume to produce an end-diastolic pressure of 10 mm Hg during baseline measurement], positive maximum dP/dt, and dP/dt at V10), diastolic function (negative maximum dP/dt), coronary blood flow, and endothelial function assessed by the coronary vascular resistance response to acetylcholine. The L -nitro-arginine methyl ester hearts showed a significantly poorer recovery ($p < 0.05$) in left ventricular function, coronary blood flow, and endothelial function than the control group. These effects of L -nitro-arginine methyl ester were reversed to equal control values by adding a 3 mmol/L concentration of L -arginine to L -nitro-arginine methyl ester. There were no significant differences in the recovery of any variables between the D-arginine and control groups. These results point to an important salutary role for the endothelial production of nitric oxide in cardiac recovery after hypothermic ischemia in neonatal lamb hearts. The mechanism of these beneficial effects of L -arginine after ischemia and reperfusion is likely due to enhancement of the endothelial production of nitric oxide. (J T HORAC C ARDIOVASC S URG 1995;109:81-7)

Arginine Metabolism: Enzymology, Nutrition, and Clinical Significance

Enteral and Parenteral Arginine Supplementation to Improve Medical Outcomes in Hospitalized Patients[1]

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ABSTRACT The amino acid L-arginine has been administered as a single supplement to humans in an effort to improve the outcome of seriously ill patients. In normal individuals, markers of collagen biosynthesis have increased with daily oral doses ranging from 14 to 24.8 g of free arginine for 14 d. No clinical evidence of improved wound healing has been reported in the few patient studies performed to date. Administration of enteral, but not intravenous, arginine has been associated with markers of improved immune function in normal individuals and in some, but not all, patient groups studied. A single study in premature infants suggested that supplementation of L-arginine (261 mg · kg^{-1} · d^{-1}) administered by both the parenteral and enteral routes decreased the incidence of necrotizing enterocolitis. A single study demonstrated that oral arginine administration in conjunction with conventional chemotherapy for active tuberculosis to HIV− but not HIV+ individuals enhanced treatment responses. In both these area, larger multicenter investigations are needed. For a difference to be a difference it has to make a difference. Supplementation of only L-arginine does not to date universally show benefit, nor does it show harm. At this time there is no rationale for the routine supplementation of arginine alone to enhance recovery from serious illness. Because of the potential for harm, this amino acid should only be administered to critically ill patients in large doses under carefully monitored study conditions. J. Nutr. 134: 2863S–2867S, 2004.

KEY WORDS: • *arginine* • *parenteral nutrition*

Arginine is a nonessential amino acid that is important in protein synthesis and plays a key role in the intermediate metabolism of nitrogen by participating in the urea cycle. Arginine can be synthesized by the body and hence dietary arginine is not essential to nitrogen economy in normal adults (1) or necessary for normal growth in children (2). However, plasma concentrations may be largely determined by nutrient supply, because synthetic machinery does not adequately compensate in response to low levels of arginine intake (3,4). In addition to its role in protein synthesis and nitrogen disposal, arginine serves as a precursor to glutamine, proline, and putrescine (via ornithine), with the latter compound participating in the synthesis of polyamines. However, the functional role that has attracted the greatest interest to physicians caring for the critically ill is the contribution of arginine in the synthesis of nitric oxide (NO). In the past 2 decades it was found that nitric oxide plays an integral role in the regulatory function of the immune system and in governing the vascular response to sepsis; henceforth, investigators have directed their efforts toward manipulating this function in an effort to enhance host responses to infection and inflammation. Administering L-arginine is one important strategy being investigated to improve the care of this patient group.

Is arginine a conditionally essential amino acid?

In young rats, cats, and dogs, arginine has been shown to be an essential nutrient and elimination of this substance from the diet can limit optimal growth (5,6). This is not the case for humans under normal circumstances. However, there may be some situations where arginine can be thought of as a conditionally essential amino acid. For example, Heird and associates (7) described 3 premature infants who received an imbalanced intravenous feeding solution composed of crystalline amino acids, free of arginine, at a dose of ~2.5 g · kg^{-1} · d^{-1}. Hyperammonemia occurred but resolved with the administration of parenteral arginine. In another study, Batshaw and associates reported that ~50% of premature infants weighing <2,500 g had elevated ammonia levels within the first 2 months of life when compared to infants weighing >2,500 g (8). When arginine and ornithine levels were compared in 2 groups of matched infants, with one group having normal ammonia levels and the other group having elevated levels, the arginine concentrations were significant lower in the hyperammonemic group. When oral arginine supplements were provided, ammonia levels fell about 25% when compared to an untreated group.

Thus, it appears that some premature infants may demon-

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strate a requirement for dietary arginine, and this may be a case of the amino acid becoming conditionally essential. Data from studies performed in both adult and pediatric patients who have sustained severe thermal injury suggest that arginine may become essential following severe injury. Yu et.al. (9,10) measured arginine kinetics in these patient groups using stable isotope tracer techniques and determined that there was little net de novo arginine synthesis, suggesting that influx of arginine was largely, if not totally, from the preformed arginine derived from proteolysis or from feeding formulas. Thus, the body does not increase the production of arginine following severe injury in order to meet the presumed increased demands.

However, in other conditions in adult humans where arginine has been administered in an attempt to enhance recovery, little evidence is available to suggest that a deficiency state exists. Rather, excessive dietary supplementation of arginine is provided to obtain a pharmacological effect from this amino acid, not to correct a nutrient deficient state.

How much arginine is enough?

Dietary arginine probably amounts to ~2–6 g/ day, depending on the level of protein intake, because arginine concentration in egg, muscle, and liver protein is ~5% of total protein (11). A variety of studies have been performed providing oral arginine supplements. Although low dose supplements in the range of 3–4 g/d have been studied (12), most investigators have given 9 or more g/d. For example, Barbul (13–15) performed 3 studies in normal volunteers giving 14, 17, and 24.8 g arginine/d for up to 2 wk with no major reported side effects. Beaumier and associates (16) gave 39.3 g/d for 6 d to normal volunteers. Other studies reported diabetic patients who received 9 g/d for up to a month (17) and investigations were carried out in subjects with HIV infection who received 19.6 g arginine/d for 14 d (18). Thus, it appears that large doses (>10 g/d) are necessary to determine specific effects and administration of this quantity has not been associated with reported side effects or toxicities.

Intravenous administration of arginine commonly occurs. Most amino acid solutions designed for parenteral nutrition contain about 8–11 g arginine/100 g amino acids (19). Thus, a 70 kg individual requiring 1.5 g amino acids $\cdot kg^{-1} \cdot d^{-1}$ would receive ~10 g arginine/d. In one study (20), L-arginine was infused alone at a dose of 20 g/d for 7 d. Parenteral arginine is administered as a constant infusion that may not stimulate the hormonal responses observed following an intravenous bolus infusion or the administration of a large oral dose of arginine. Specialized amino acid solutions are available for patients in renal and hepatic failure but arginine is generally omitted from such mixtures or the concentration of this amino acid is greatly reduced.

Clinical utility—wound healing

In a variety of laboratory studies, supplemental arginine administration has enhanced wound healing in animals, particularly rodents. In 1990 Barbul and associates (13) reported the effects of administration of supplemental arginine on collagen deposition and immune function in healthy volunteers. All individuals had small polytetraflouroethylene catheters inserted subcutaneously into the right deltoid region to be harvested later and assessed for collagen ingrowth and biosynthesis. The subjects were randomized into 3 groups; the first received 30 g arginine hydrochloride/24 h (which contained 24.8 g free arginine), the second received 30 g arginine aspartate (17 g free arginine) daily, and the third received placebo. The supplement volunteers consumed an oral diet ad libitum for 2 wk, at which point the catheters were removed and the contents analyzed for hydroxyproline content, which was used as an index of synthesis of new collagen. Arginine supplementation enhanced the amount of hydroxyproline in the catheters with the placebo group having 10.1 ± 2.32 nmol/cm graft vs. 17.57 ± 2.16 in the arginine asparate group and 23.85 ± 2.16 in the arginine hydrochloride group ($P < 0.02$ for both arginine groups vs. placebo, data presented as means ± SEM). Simultaneously, lymphocyte mitogenesis increased in both supplemented groups in response to standard stimuli.

In a similar study (14), investigators from the same laboratory studied the effect of arginine administration on wound healing in healthy elderly individuals (>65 y of age). Thirty individuals received 30 g arginine aspartate (containing 17 g free arginine) and 9 subjects served as controls and received placebo. After 2 weeks of supplementation, the hydroxyproline content in the subcutaneous catheters in the supplemented group was about 50% greater than in the placebo controls. Arginine administration did not influence the DNA content in the catheters or the rate of epithelialization of the skin defect. In addition to improved mitogesis, serum insulin-like growth factor-1 was elevated in the group receiving arginine.

In a more recent study (15), arginine (14 g) was administered with a mixture of other substances (B-hydroxy-B-methylbutyrate and glutamine) in a blinded study in elderly volunteers. Similar endpoints were followed and the normal subjects that received the specialized mixture demonstrated increased rates of collagen deposition. It was not determined which substance was the active component in the mixture.

Associated with these wound-healing studies in normal volunteers, a variety of endpoints have been monitored to evaluate safety associated with arginine administration (21,22). The protocols did not provide for neutral observers to follow a detailed assessment protocol to determine complications and toxicities associated with arginine administration. However, the investigators reported few side effects and/or associated complications with the arginine doses administrated. Initially, gastrointestinal disturbances were noted, but these resolved by administering the amino acid in divided doses throughout the day.

In summary, administering arginine to normal volunteers for 2 wk improved collagen synthesis, as determined by a surrogate marker of collagen deposition in a plastic tube implanted in the subcutaneous tissue. This finding was observed in both middle aged and elderly individuals; the latter group is known to have prolonged rates of wound healing. However, while these studies are encouraging, there is no data that demonstrate that supplemental arginine actually improves healing of wounds sustained following an injury or operation and thus enhances clinical outcome in patients. These clinical studies are necessary to conclude that arginine should be utilized for this indication.

Arginine in tube feedings

In addition to using arginine as an oral supplement, this amino acid has been administered to seriously ill patients via a feeding tube along with other dietary constituents. One of the first studies utilizing this approach was reported by Daly et al. (23), who determined the effect of arginine on the immune and metabolic responses in 30 patients with cancer of their upper gastrointestinal tract who underwent surgical resection. In the postoperative period, patients received tube feedings supplemented with either L-arginine (25 g/d) or L-glycine (43 g, which served as an isonitrogenous control). Over the 7 d of

study, nitrogen balance was similar in the 2 groups but T-lymphocyte activation increased significantly in the arginine group at day 4 and 7 postoperatively, when compared with the glycine group. However, respiratory, infectious, and gastrointestinal complications were comparable in the 2 small groups of patients (**Table 1**). These same findings were rereported in a subsequent publication (24) that appeared 2 years later in the critical care literature.

Two studies have been reported using arginine supplemented enteral diets in patients with head and neck cancer. In the first study (25), Riso and associates randomized 44 patients at operation into 2 groups. Twenty-three patients received the arginine-enriched diet and 21 received an isocaloric isonitrogenous control formula. The patients received 1.5 g protein $\cdot kg^{-1} \cdot d^{-1}$ and the enriched diet contained about 10% of the protein as arginine. The 2 groups were well matched and underwent comparable surgical procedures. The side effects of the tube feedings were also comparable in the 2 groups. Although there were some enhanced immunological responses detected in the supplemented group, there was no difference between the 2 groups when evaluating postoperative complications or length of stay (**Table 2**).

In another report (26), authors studied 49 patients with head and neck cancer who were severely malnourished (>10% weight loss). The subjects were randomized into 1 groups and received 9 d of preoperative nutrition, with or without arginine supplementation. The authors studied these patients extensively but concluded that 9 d of preoperative tube feeding, with or without arginine with continued administration into the postoperative period, did not significantly improve nutritional status, reduce the surgery-induced immune suppression, or affect clinical outcome in severely malnourished head and neck cancer patients.

Studying critically ill patients, Preiser and associates (27) focused their investigations in individuals receiving long-term enteral tube feedings. Of the 37 patients who completed the 7-d study, 20 received a formula enriched with free arginine (6.3 g/L) and 17 received an isocaloric and isonitrogenous arginine-free control solution. Blood and urine was obtained to determine the effects of arginine supplementation on nitric oxide production and amino acid concentrations.

The plasma concentrations of arginine and ornithine increased significantly in the arginine-supplemented group (from 55 ± 9 mmol/L to 102 ± 9 and from 57 ± 7 to 135 ± 11, respectively, mean ± SEM) and no alterations in these concentrations were detected in the patients who received the control formula. There were no differences between groups in either nitric oxide production or plasma phenylanlanine concentration (the latter used as an index of protein catabolism).

Several conclusions can be made from these studies of arginine supplemented enteral feedings. First, glycine was used in several studies as a control for arginine administration. Glycine has both metabolic and immunological effects and when administered in the large doses reported (e.g., 43 g/d) this substance should not be considered an inert control. This design flaw makes these studies extremely difficult to interpret because no true control data are available for comparison of the arginine effects. Secondly, no studies using arginine as a single supplement reported improved outcome, although increases in in vitro immunological functions were observed in studies in normal volunteers and in some, but not all, studies in patients. Lastly, a carefully performed metabolic study showed that enterally administered arginine was absorbed and appeared to be metabolized mainly to ornithine.

TABLE 1

Complications following enteral arginine supplementation in patients following resection of gastrointestinal cancers[1]

	Control (n = 14)	Arginine (n = 16)
Total no. of complications	9	10
Respiratory complications	5	5
Temp >38°C	6	4
Nausea	2	2
Diarrhea	4	4
Cramping and bloating	6	4

[1] Reflects number of patients, from ref 23.

TABLE 2

Complications and length of stay in patients with cancer of the head and neck receiving two diets[1]

	Control (n = 21)	Arginine supplemented[2] (n = 23)
Flap necrosis	1	0
Fistula	1	1
Purulent drainage	3	2
Length of stay (days)	28 ± 12	25 ± 12

[1] Indicates number of patients or days presented as mean ± SD.
[2] No differences were observed between groups, from ref 25.

Arginine in the treatment of active tuberculosis

In a randomized double-blind study, adults with smear-positive tuberculosis were randomized to receive arginine or placebo in addition to conventional chemotherapy for 4 wk (28). The primary endpoints were conversion of sputum to negative status, weight gain, and improvement of symptoms. Biochemical endpoints were also monitored. A significant positive clinical response was noted in the HIV− patients who received the arginine supplement but not in the HIV+ supplemented patients. The authors conclude that this effect is likely mediated by the increased production of nitric oxide, which is known to be involved in the host defense against tuberculosis.

Arginine for the prevention of necrotizing enterocolitis in the premature infant

A significant number of premature infants develop inflammation of the intestinal tract, referred to as necrotizing enterocolitis (NEC), early in life. It has already been noted that many premature infants have low levels of arginine, and subsequent studies have associated low arginine plasma concentrations with NEC (29,30). To determine whether supplementation of arginine could reduce NEC in premature infants, Amin and associates studied 152 premature infants weighing <1250 g (31). The infants were prospectively randomized into 2 groups, one received arginine (1.5 mmol $\cdot kg^{-1} \cdot d^{-1}$ equilivent to 261 mg $\cdot kg^{-1} \cdot d^{-1}$) and the other a low arginine diet. The arginine was initially added to the parenteral feedings but when enteral feeds reached 40% of the infant's requirement the arginine was given by the enteral route.

The patients were well matched on entry to the study and otherwise received comparable care. NEC developed in 5 infants receiving arginine and in 21 infants receiving placebo ($P < 0.001$). Arginine concentrations increased in the study

group, but no other differences occurred between the 2 groups when comparing nutrient intake or plasma amino acid concentrations. Other complications were similar between the 2 groups, and this included the number of days required on a ventilator, the incidence of interventricular hemorrhage, and the occurrence of sepsis (**Table 3**).

This area of study improves our understanding of the role that nutrients play in intestinal development, and such an approach is potentially helpful in improving outcome of premature infants using a low cost nutrient with little apparent toxicity. However, NEC is an extremely difficult disease to diagnose, quantitate, and treat, and the occurrence of the disease is quite sporadic and the incidence highly variable. These issues have raised a note of caution by experts in the field who have evaluated these data (32). A much larger multicentered trial has been called for to evaluate the use of arginine in the prevention of NEC.

Arginine supplementation in intravenous formulas

As previously noted, arginine is present in most balanced intravenous formulas, and represents about 10% of the amino acids infused; patients on average will receive about 10 g of arginine/d. Few long-term studies have been performed supplementing intravenous diets with arginine above these levels. Short-term studies have infused L-arginine at rates ranging between 0.5 and 0.525 $g \cdot kg^{-1} \cdot 30\ min^{-1}$, and investigators (33) have examined responses to these infusions in infants with persistent pulmonary hypertension and adults with salt sensitive and essential hypertension, to name a few of the many protocols reported in the literature.

Two investigations examined the effects of arginine supplementation in designing intravenous amino acid solutions. In a classic study by Vinners, Furst, and associates (34), the nutritive effects of nonessential amino acids were studied in normal individuals. These investigators found that arginine had the highest nutritive value of all nonessential amino acids tested, although it competed with lysine for renal excretion (a topic which will be discussed later). These investigators concluded that arginine should be included in balanced solutions to prevent hyperammonemia, and they recommended an infusion of 6 g/d.

In a more recent study, Berard et al. (35) infused a standard balanced amino acid solution to critically ill patients and then altered the solution composition based on variations in the plasma aminogram. The investigators found that variations in arginine concentrations after the initial 3 d of infusion of a balanced amino acid formula were always associated with abnormal variations in lysine concentrations. The data demonstrated that the excessive infusion of lysine impaired arginine metabolism and that by reducing the lysine supply the concentration of arginine would be normalized.

Three other arginine infusion studies deserve mention. Sigal et al. (20) infused 20 g of arginine hydrochloride daily (given with no other amino acids) into postoperative surgical patients for 7 d and compared the outcome to a matched group of patients receiving a balanced amino acid formula (Travasol; Baxter). The plasma arginine and ornithine levels rose in the arginine infusion group from 49 ± 16 to 228 ± 50 and from 31 ± 16 to 191 ± 76, respectively (mean ± SD), and did not change significantly in the controls. Nitrogen balance was similar in the 2 groups over the 7-day study period. Lymphocyte proliferation fell in both groups and there were no differences in immune responses between groups. Thus, when arginine was infused without adequate calories or other amino acids, no enhancement of mitogen-stimulated lymphocyte proliferation was observed.

In a somewhat similar study, Song and associates (36) monitored immune responses in patients with colorectal cancer undergoing resection. In the group receiving 20 g arginine supplemented in their parenteral nutrition, immune responses were improved compared to the nonsupplemented group. No outcome differences were noted.

In the third study (37), arginine and glutamate were added to standard nutritional solutions in an attempt to provide glutamine precursors. The amount of arginine present in the study solution was about 50% greater than that present in the control. Plasma concentrations of arginine increased in the supplemented group and there was a significant relation between concentrations of arginine and glutamine ($r = 0.45$, $P < 0.01$). This association was not found in the patients receiving the control solutions. During the study the incidence of infection increased from 7/20 to 8/20 in the group receiving the standard solution and from 3/17 to 8/17 in the patients receiving the enriched formula. The 28-d mortality was 6/17 in the control group and 8/20 in the arginine-enriched formula group.

In conclusion, a variety of infusion studies using supplemental arginine were performed but the outcome in seriously ill hospitalized patients was not altered.

The safety of arginine

Supplemental arginine has been provided in a variety of clinical situations, including administration to patients with cancer. Some animal studies suggest that arginine administration will reduce tumor growth. However this approach is controversial. In a human study, patients with breast cancer received either a standard diet or a diet containing supplemental arginine (30 g/d) for 3 d before operation (38). At the time of surgery, the rate of protein synthesis within the tumor was determined using stable isotope techniques and tumor tissue was stained to determine the presence of the activation antigen Ki67. The median rate of tumor protein synthesis was 10%/d in the control patients and 25.6% in patients receiving arginine supplements ($P < 0.005$). The rates of protein synthesis correlated with the Ki67 expression, confirming that tumor cells, rather than cellular infiltrate, accounted for the changes observed.

As a result of this and other data, one recent review (33) stated, "long-term data regarding the impact of arginine supplementation on mortality are not available. It has been suggested that this is probably a result of persistent concern about the possible promotion of tumor growth in some cases."

In work previously mentioned, Vinners and co-workers

TABLE 3

Complications which occurred in arginine-supplemented infants and controls[1]

	Controls ($n = 77$)	Arginine supplements ($n = 75$)
NEC	21	5[2]
Deaths	0	3
Median days on ventilator	4	5
Intraventricular hemorrhage[3]	3	3
Sepsis	11	9

[1] Indicates number of patients.
[2] $P < 0.001$, no significant differences between groups were observed in the other endpoints, from ref 32.
[3] >Grade II at follow-up.

(34) examined the effect of arginine infusion along with other amino acids in normal individuals. With infusion of arginine at varying doses there was increased urinary excretion of the amino acid lysine. This occurred because arginine competed with lysine for tubular reabsorption and thus augmented the renal excretion of this particular amino acid. The infusion of about 10 g of arginine/d provoked the excretion of about 10% of the amount of lysine administered. Administration of large doses of arginine should not occur over the long term without consideration that imbalances of other amino acids may occur.

Finally, it is important to mention that immunomodulatory enteral diets containing arginine (about 12 g/L) and other supplements "may be associated with excess mortality in some subgroups of critically ill patients" (39). Those who have reviewed these data "hypothesize that systemic inflammation might be undesirably intensified by immune-enhancing nutrients like arginine in critically ill patients" and they recommend that patients with the inflammatory response syndrome should not receive immune-enhancing substrates (40). The data have recently been reviewed by a professional group who concluded that there was insufficient data to recommend that these enteral formulas containing agrinine and other immunoactive substances be administered to critically ill patients in intensive care units (41). Until more carefully executed studies are published, a strong clinical recommendation cannot be made at this time for delivering arginine-supplemented diets to seriously ill patients. Such immunomodulatory diets should only be administered to critically ill patients under carefully controlled circumstances with a process in place to objectively monitor toxicities and outcome.

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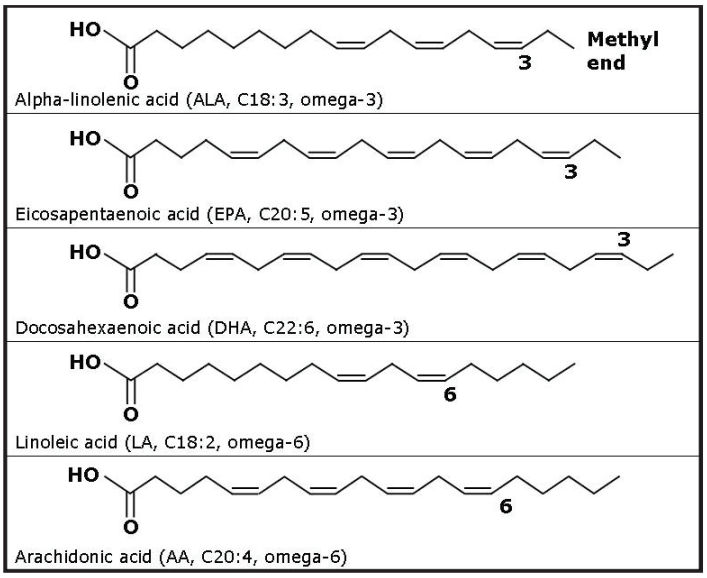
3. Fatty acids

Essential fatty acids serve as components of nerve cells, cellular membranes, and the very important regulatory substances known as prostaglandins.

Omega fatty acids are termed essential, as they cannot be produced by the pet's body. These essential fatty acids must be consumed in a healthy balanced diet, and there is a good chance that the pet may not be receiving everything he or she needs in commercial pet food.

Fatty acid supplements contain two classes of polyunsaturated fats: omega-3s and omega-6s.



Omega-3 fatty acids include:
- Alpha-linolenic acid (ALA)
- Docosahexaenoic acid (DHA)
- Eicosapentaenoic acid (EPA)

Omega-6 fatty acids include:
- Arachidonic acid (AA)
- Dihomo-gamma-linolenic acid (DGLA)
- Gamma linolenic acid (GLA)
- Linoleic acid (LA)

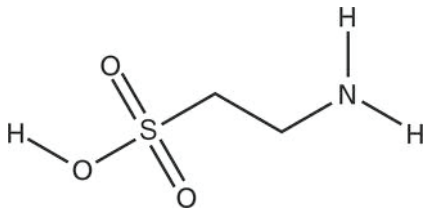
Potential health benefits of fatty acid supplementation include:
- Allergies – may prevent allergies developing among young animals in response to inhaled substances like mold or pollen, as well as treating skin conditions caused by allergies, such as miliary dermatitis and eosinophilic granulomas.
- Arthritis – reduce inflammation.
- Autoimmune conditions – lessen harmful effects on the body.
- Cancer – omega-3s slow development of certain cancers (though omega-6s can stimulate faster growth of tumours).
- Cholesterol and plasma triglycerides – decrease blood levels of cholesterol and triglycerides, reducing risk of heart disease.
- Eyes – aid proper development of visual cortex and retinas.
- Hyperlipidemia – a condition that sometimes afflicts animals receiving synthetic derivatives of vitamin A (retinoid therapy) – fish oil supplements may provide benefits.
- Kidney disease – may help prevent or slow progression.
- Seborrhea – this flakey skin condition may be caused by a deficiency in a certain fatty acid – supplementation can mitigate its effects.
- Ulcerative colitis and inflammatory bowel disease – reduces inflammation.
- Yeast infection – slows growth of Malassezia pachydermatis, which commonly afflicts cats and dogs.

Fatty acids for dogs are not medicines and, when used in isolation, cannot cure diseases such as kidney failure or cancer. However, used in complement with other medication, they can facilitate speedier recovery and improved health conditions.

Pain control also improves the pet's recovery time and speeds the healing process. Pain and inflammation tend to go hand in hand. That's because inflammation is the body's natural response to an injury. It serves a vital purpose protecting the injured area by rushing fresh blood, antibodies, and nutrients to the area for healing. A natural option for fighting pain from chronic inflammation without the risks of NSAIDs is by increasing the intake of Omega-3 essential fatty acids.

4. Taurine

Taurine helps fight cellular agressions induced by oxidative stress and promotes good health of the immune system. Its most important roles are in bile acid conjugation, retinal function, and normal functioning of the myocardium. Taurine also appears to be necessary for healthy reproductive performance in dogs and cats.



Interventional nutrition for cardiac disease.
Freeman LM
Clin Tech Small Anim Pract, 1998 Nov, 13:4, 232-7

Abstract
Animals with cardiac disease can have a variety of nutritional alterations for which interventional nutrition can be beneficial. Deviation from optimal body weight, both obesity and cachexia, is a common problem in cardiac patients and adversely affects the animal. Methods for maintaining optimal weight are important for good quality of life in dogs and cats with cardiac disease. Providing proper diets to prevent excess intake of sodium and chloride also is important, but severe salt restriction may not be necessary until later stages of disease. Certain nutrient deficiencies may play a role in the pathogenesis or complications of cardiac disease, but nutrients also may have effects on cardiac disease which are above and beyond their nutritional effects (nutritional pharmacology). Supplementation of nutrients such as taurine, carnitine, coenzyme Q10, and omega-3 polyunsaturated fatty acids may have benefits in dogs or cats with cardiac disease through a number of different mechanisms. By addressing each of these areas maintaining optimal weight, avoiding nutritional deficiencies and excesses, and providing the benefits of nutritional pharmacology, optimal patient management can be achieved.

Activity of N-chlorotaurine against herpes simplex- and adenoviruses.
Nagl M; Larcher C; Gottardi W
Antiviral Res, 1998 Apr, 38:1, 25-30

Abstract
N-chlorotaurine, an essential weak oxidant produced by stimulated human leukocytes, is known to have bactericidal, fungicidal and vermicidal properties. This study for the first time demonstrates its virucidal activity. By viral suspension tests at incubation times between 5 and 60 min, virus titers of both Herpes simplex virus type 1 and 2 were reduced about 1.3-2.9 log10 and 2.8-4.2 log10 by 0.1 and 1%, (5.5 and 55 mM) N-chlorotaurine, respectively. Virus titer reduction of adenovirus type 5 between 15 and 60 min was 0.5-2.0 and 0.6-4.0 log10, respectively, by the same concentrations of N-chlorotaurine. These findings support a contribution of N-chlorotaurine in destruction of pathogens during inflammatory reactions and also the possibility of its application as an antiviral agent in human medicine.

Prevention of liver failure in parenteral nutrition-dependent children with short bowel syndrome.
Meehan JJ; Georgeson KE
J Pediatr Surg, 1997 Mar, 32:3, 473-5

Abstract
Progressive liver failure in parenteral nutrition (PN)-dependent children with short bowel syndrome carries significant morbidity and mortality. The authors retrospectively reviewed 47 consecutive patients with short bowel syndrome diagnosed from October 1985 through October 1995. All patients were treated according to a protocol designed to promote intestinal motility and discourage bacterial translocation. Elements of the protocol included the use of taurine, vigilant prevention and aggressive treatment of sepsis, meticulous catheter care, early PN cycling, appropriate enteral feeding, and measures designed to inhibit gastrointestinal bacterial translocation, especially gram-negative rods. Complete blood counts and serum liver function studies were compiled from both clinic visits and hospital admissions for each patient every 3 to 6 months while they were on PN. Three patients were lost to follow-up after they had moved out of state. The length of time on PN ranged from 3 months to 9.4 years with an average of 2.2 years. Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glutamyltransferase (GGT) were present in 82%, 66%, and 84% of patients, respectively. Alkaline phosphatase was elevated in 58% of patients. Eight patients (18%) are still on PN, and 31 (70%) have been weaned off PN. Five patients have died (11%). Three patients (7%) developed cholecystitis requiring cholecystectomy. No patients developed progressive liver failure. These results suggest that PN-related liver failure may be prevented in most patients with short bowel syndrome. Specific measures to prevent PN-related cholestatic jaundice need further investigation.

Effects of taurine on the motility and intracellular free Ca2+ concentration of fowl spermatozoa in vitro.
Barna J; Ashizawa K; Boldizsár H; Inoue M
J Reprod Fertil, 1998 Nov, 114:2, 225-9

Abstract
The effects of taurine on the motility and intracellular free Ca2+ concentration of fowl spermatozoa were investigated in vitro. The addition of taurine, within the range of 0-5 mmol l(-1), did not appreciably affect the motility of intact fowl spermatozoa. Motility remained almost negligible at 40 degrees C, while vigorous movement was observed at 25 degrees C. Even with the addition of Ca2+ before the addition of taurine, neither stimulation nor inhibition of motility was observed compared with the control (no addition of taurine). Similar results were obtained by the addition of taurine and calyculin A, a specific inhibitor of protein phosphatases. There were no changes in intracellular free Ca2+ concentrations, measured by a fluorescent Ca2+ indicator, fura-2, in taurine-treated spermatozoa. These results suggest that taurine is not involved in the regulation of fowl sperm motility and metabolism by intracellular Ca2+ mobilization in vitro.

Taurine content in Chinese food and daily intake of Chinese men.

Zhao X; Jia J; Lin Y
Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine, Beijing, P.R. China.
Adv Exp Med Biol, 1998, 442:, 501-5

Abstract

The taurine content in Chinese food, including seafood, fresh water fish, meats and some plants, was examined in this study. Seafood was freshly collected from 4 coastal areas in China. Meat and plant food samples were obtained from food markets. The highest concentration of taurine was found in crustaceans and molluses (300-800 mg per 100 g edible portion). The amount of taurine in fish was variable. Beef, pork and lamb contained taurine in concentrations ranging from 30-160 mg per 100 g. No taurine was detected in hen eggs and plants. The daily taurine intake of representative Chinese men (18-45 years old, 60 kg body weight, light physical activity) was also studied in 1990 as a part of the Total Diet Study. Representative food samples were collected from 12 provinces in 4 areas of China. Samples were then combined and cooked according to food categories (meat, seafood, vegetables, etc) The combined meat and seafood samples were analyzed for taurine. The daily taurine intake of a standard man in the 4 areas was calculated based on the amount of food intake obtained from the dietary survey and the taurine concentration in the analyzed food samples. The result showed that the daily taurine intake of a standard Chinese man in the 4 different test areas ranged from 34 to 80 mg per day.

The effect of dietary sulfur-containing amino acids on calcium excretion.

Wang XB; Zhao XH
Adv Exp Med Biol, 1998, 442:, 495-9

Abstract

The relationships between dietary protein and sulfur amino acid (methionine and cystine or taurine) intakes and urinary calcium excretion were examined both in animals and in young men. Thirty-two adult Wistar rats were divided into 4 groups, i.e., basal diet (group I), supplemented with albumin (II), methionine and cystine (III), or taurine (IV). During the 5-week feeding period, food consumption was recorded and 48 h urine samples were collected 4 times for each rat. Urinary calcium, creatinine and sulfate were measured. The results showed that the calcium and sulfate excretion in rats in group II and III were significantly higher than rats in the basal diet group. In contrast, supplementing a basal diet with taurine did not increase sulfate excretion and failed to induce hypercalciuria. The same result was also observed in the study carried out in Chinese young men. An increase in protein intake from 67 g to 107 g caused an increase in urinary calcium and sulfate. Supplementation with methionine and cystine in an amount to simulate those in the high protein diet had a similar effect. Adding taurine to the diet had no effect on urinary calcium and sulfate excretion. About 60 percent of the supplemented taurine in the diet was detected in the urine.

Plasma concentration of taurine is higher in malnourished than control children: differences between kwashiorkor and marasmus.

Lima L; Jaffé E
Adv Exp Med Biol, 1998, 442:, 487-94

Abstract

Plasma free amino acids were determined in the plasma of severely malnourished children under two years of age. A total of thirty-one patients and eleven controls were evaluated: seventeen cases of kwashiorkor, eight cases of marasmus, and six cases of marasmic-kwashiorkor. Fasting plasma samples were taken in the morning on the day of admission. Fasting plasma samples were also taken from nine patients at discharge after two months in the hospital where they received a balanced diet as treatment. A partial reversal of the signs of malnutrition was observed at discharge. In the whole group of patients ad admission, lower concentrations of tyrosine, methionine, tryptophan, and leucine and higher concentrations of aspartate, glutamate, and taurine were observed compared to controls. Taurine continued to be elevated in the malnourished group at the time of discharge. Marasmic children, as compared to controls, had high aspartate and low tryptophan levels, but taurine levels were not significantly different from controls. Kwashiorkor patients had low tyrosine, methionine, tryptophan, and lysine, and significantly higher taurine plasma levels. The elevated concentration of taurine might be the result of a redistribution of this amino acid to provide specific tissues with the required amount for development.

The role of taurine in infant nutrition.
Chesney RW; Helms RA; Christensen M; Budreau AM; Han X; Sturman JA
Adv Exp Med Biol, 1998, 442:, 463-76

Abstract
The importance of taurine in the diet of pre-term and term infants has not always been
clearly understood and is a topic of interest to students of infant nutrition. Recent evidence indicates that it should be considered one of the “conditionally essential” amino acids in infant nutrition. Plasma values for taurine will fall if infants are fed a taurine-free formula or do not have taurine provided in the TPN solution. Urine taurine values also fall, which is indicative of an attempt by the kidney to conserve taurine. The very-low-birth-weight infant, for a variety of reasons involving the maturation of tubular transport function, cannot maximally conserve taurine by enhancing renal reabsorption and, hence, is potentially at greater risk for taurine depletion than larger pre-term or term infants, and certainly more than older children who have taurine in their diet. Taurine has an important role in fat absorption in pre-term and possibly term infants and in children with cystic fibrosis. Because taurine-conjugated bile acids are better emulsifiers of fat than glycine-conjugated bile acids, the dietary (or TPN) intake has a direct influence on absorption of lipids. Taurine supplementation of formulas or TPN solutions could potentially serve to minimize the brain phospholipid fatty acid composition differences between formula-fed and human milk-fed infants. Taurine appears to have a role in infants, children, and even adults receiving most (>75%) of their calories from TPN solutions in the prevention of granulation of the retina and
electroencephalographic changes. Taurine has also been reported to improve maturation of auditory-evoked responses in pre-term infants, although this point is not fully established. Clearly, taurine is an important osmolyte in the brain and the renal medulla. At these locations, it is a primary factor in the cell volume regulatory process, in which brain or renal cells swell or shrink in response to osmolar changes, but return to their previous volume according to the uptake or release of taurine. While there is a dearth of clinical studies in man concerning this volume regulatory response, studies in cats, rats, and dog kidney cells indicate the protective role of taurine in hyperosmolar stress. The infant depleted of taurine may not be able to respond to hyper- or hyponatremic stress without massive changes in neuronal volume, which has obvious clinical significance. The fact that the brain content of taurine is very high at birth and falls with maturation may be a protective feature, or compensation for renal immaturity Defining an amino acid as “conditionally essential” requires that deficiency result in a clinical consequence or consequences which can be reversed by supplementation. In pre-term and term infants, taurine insufficiency results in impaired fat absorption, bile acid secretion, retinal function, and hepatic function, all of which can be reversed by taurine supplementation. Therefore, this small beta-amino acid, taurine, is indeed conditionally essential.

Taurine can ameliorate inflammatory bowel disease in rats.
Son M; Ko JI; Kim WB; Kang HK; Kim BK
Adv Exp Med Biol, 1998, 442:, 291-8

Abstract
We previously reported that the protective effect of taurine against indomethacin-induced gastric mucosal injury was due to its antioxidant effects which inhibited lipid peroxidation and neutrophil activation. In this study, we examined the effect of taurine on reducing the inflammatory parameters of trinitrobenzene sulfonic acid (TNBS)-induced inflammatory bowel disease (IBD) in rats. To induce IBD, rats were given ethanolic TNBS intracolonically. The rats then received 500 mg/kg/day of taurine per orally. The rats were sacrificed one week after IBD induction. Ulceration and inflammation of the distal colon with formation of granuloma in the vehicle-treated IBD rats after two days of administration of TNBS were observed. Treatment with 0.5 g/kg of taurine by the oral route ameliorated colonic damage and decreased the incidence of diarrhea and adhesions. Colon weight (an index of tissue edema) was markedly increased in the IBD rats after administration of TNBS, but was significantly lower after taurine treatment. Myeloperoxidase (MPO) activity in the vehicle-treated IBD rats was substantially increased compared with that of the control. The taurine-treated animals showed reduced MPO activity (35% lower) when compared with that of the vehicle-treated animals. Taurine treatment decreased basal and formyl-methionyl leucyl phenylalanine (FMLP) stimulated reactive oxygen generation in colonic tissue of the IBD rat compared with vehicle treatment after one week. These results suggest that administration of taurine reduced the inflammatory parameters in this rat model of IBD by increasing the defenses against oxidative insult.

Cardiac actions of taurine as a modulator of the ion channels.

Satoh H

Adv Exp Med Biol, 1998, 442:, 121-8

Abstract

During ischemia, hypoxia and cardiac failure, the heart undergoes several adverse changes, including a reduction in taurine (2-aminoethanesulfonic acid). Oral administration of taurine under these disease conditions would be expected to act like a mild cardiac glycoside. Taurine would exert improvement in the accumulation of [Na]i and the loss of alpha-amino acids. Nonetheless, when intracellular taurine content is raised, there would be the benefit of increased Ca2+ release from the sarcoplasmic reticulum and increased Ca2+ sensitivity of the contractile proteins, as well as possible changes in the action potential associated with the actions of taurine on ion channels. In fact, intracellular application of taurine produces the opposite actions to extracellularly administration of the amino acid. From our previous experiments, the electrophysiological actions of taurine on cardiac muscle cells include the following. (a) Prolongation of action potential duration (APD) at high [Ca]i and shortening of APD at low [Ca]i. In multicellular preparations, however, taurine did not always prevent [Ca]o-induced effects. (b) Stimulation of spontaneous activity at low intracellular and extracellular Ca2+ concentrations ([Ca]i and [Ca]o), and vice versa. (c) Inhibition of the L-type Ca2+ current (ICa(L)) at high [Ca]i, and vice versa. (d) Enhancement of the T-type Ca2+ current (ICa(T)). (e) Inhibition of fast Na+ current (INa). (f) Enhancement of TTX-insensitive slow Na+ current. (g) Inhibition of delayed rectifier K+ current (IKrec) at high [Ca]i, and vice versa. (h) Enhancement of the transient outward current (Ito). (i) Inhibition of the ATP-sensitive K+ current (IK(ATP)). Since taurine acts on so many ion channels and transporters, it is clearly non-specific. Although it is very difficult to understand the diversity of taurine's actions, it is possible that taurine can exert its potent cardioprotective actions under the conditions of low [Ca]i, as well as Ca2+ overload. Thus, although taurine-induced modulation of ion channels located on the cardiac cell membrane is complex, the multiple effects may combine to yield useful therapeutic results