

Therapeutic Uses of Amino Acids

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The utility of amino acids in medicine today continues to be explored via clinical research and applications. Amino acids have several roles in the body; as the building blocks of protein, amino acids are found throughout the body. Muscle is by far the most protein- and amino acid-rich tissue in the body.¹ Health care practitioners are gaining more knowledge about amino acids, including their metabolism in the body, imbalances, and chemical structures.

Therapeutic use of amino acids presents natural medicine with an important therapeutic option. Some of the most prominent therapeutic applications of amino acids are for treatment of imbalances of brain metabolism and neurotransmission. Other primary areas in which amino acids are important include gastrointestinal (GI) health, immune function, and cardiovascular health.

Amino acids are classified as essential, nonessential, or conditionally essential, according to whether the body is able to synthesize the amount that it needs for metabolic maintenance. Incomplete intake of amino acids may predispose a patient to many symptoms, the most obvious of which are growth retardation and weight loss. Overall, amino acids are required daily by the human body because they are not stored for long periods of time nor in adequate amounts to sustain health.

Glutamine

One of the most freely available amino acids in the body, glutamine is derived mainly from skeletal muscles. The liver, kidneys, GI tract, and immune system utilize glutamine readily. Inside the organs, glutamine transports nitrogen and carbon.¹ Regarded mainly as nonessential (the body can manufacture some amount), glutamine is essential for proper immune system function and GI integrity (adequate amounts are produced by the intestinal mucosa, but not in amounts necessary in times of extreme physiologic stress), and plays a role in maintaining overall amino-acid balance in the body. Because of these essential roles, glutamine should, more appropriately, be considered a conditionally essential amino acid.²

Gastrointestinal Health: Oral Mucositis

Oral ingestion of glutamine is useful for treating mucositis, an inflammatory condition of the mucous membranes that often results from chemotherapy or radiation therapy. Glutamine treat-

ment can reduce the development and severity of mucositis and can shorten the duration of mouth pain in patients undergoing the aforementioned therapies.³

Glutamine supplementation is a highly cost-effective treatment for patients who undergo cancer treatments.

In addition to chemotherapy-induced anorexia, painful sores in the oral mucosa can make eating an unpleasant or even intolerable experience for these patients who desperately need good nutrition during the course of therapy. Providing glutamine for such patients, and healing their mucositis, can improve their quality of life at a time when such support is much needed.

It has been demonstrated that glutamine is found in reduced amounts in certain cancers.⁴ Coupled with the fact that GI cells are some of the most rapidly dividing cells in the body, and that chemotherapy (as a side-effect) targets these rapidly dividing cells, patients are at an increased risk of developing GI problems. Glutamine supplementation can help prevent GI toxicity induced by chemotherapy and radiation, thereby assisting normal GI function.⁵

Glutamine is a preferential metabolic substrate for the enterocytes and is thought to play a regulatory role in the intestinal tissue by influencing cellular proliferation and differentiation.⁶ As a result, the GI tract is the largest consumer of glutamine in the body⁷; suboptimal dietary amounts of glutamine can lead to atrophic changes, including ulceration and necrosis of the intestinal tissue.

Immune Function

Similar to the cells of the GI system, certain cells of the immune system also utilize glutamine preferentially during times of unusual stress. Even at times of relative physiologic normalcy, lymphocytes and macrophages consume glutamine at high rates.⁸

The intricate relationship between skeletal muscle glutamine stores and plasma levels of this amino acid is thought to influence immune function directly. Muscular overuse can lead to reduced levels of glutamine in the plasma and, thereby, may have a negative effect on lymphocyte function.

The “glutamine hypothesis” suggests that, at times when muscular cells are under intense and prolonged physical stress, the demand for glutamine in the muscle itself and in other organs may leave the lymphoid system in a state of relative glutamine scarcity. This is supported by studies that demonstrate a sharp decline in plasma glutamine concentration following long-term physical stress.⁹ Low plasma levels of glutamine are associated with overtraining as well.¹⁰

Given this evidence, however, some studies^{11,12} have demonstrated that, even though glutamine supplementation was able to offset postexercise drops in glutamine levels, postexercise immunodeficiency was not significantly altered. Researchers are still not certain if the quantitative decline in plasma glutamine is actually great enough to compromise immune-cell function or if *intracellular* glutamine concentrations are reduced because of declining plasma levels postexercise.

Because of this uncertainty, some researchers speculate that the glutamine hypothesis explains immune function decline in relation to stressful conditions adequately but low plasma levels following exercise do not entirely explain postexercise immunodeficiency.¹³ Despite these findings, the literature is full of evidence that supports the need for exogenous glutamine supplementation in maintaining immune function in very ill patients and the utility of this amino acid in supporting muscle protein mass.

When given to endurance athletes, glutamine was able to reduce the incidence of self-reported illness significantly.¹⁴ "Immune function" itself is a hugely broad term and, thus, simply stating that glutamine benefits the immune system is a very nonspecific claim. More research points to neutrophils as possible immune-system beneficiaries specific to glutamine supplementation.¹⁵ The majority of studies using glutamine for immunodeficient conditions used doses ranging from 3 to 6 g per day at a minimum. Other studies have used amounts ranging from 500 mg/kg per day in patients with radiation mucositis¹⁶ to 40 g per day in patients¹⁷ with HIV.

Glycine and Dimethylglycine

Glycine is a nonessential amino acid and is derived (in the body) from serine. Typically, a person may consume roughly 2 g of glycine as part of a standard diet (rich in meat, fish, legumes, and dairy products). Glycine is transported easily into the brain and acts primarily as an inhibitory neurotransmitter. Brain concentrations of glycine are mainly stable with an adequate diet; however, supplemental intake can bolster central nervous system concentrations.¹⁸

Glycine binds avidly with receptors in the locus ceruleus, a group of cell bodies located in the pons of the midbrain. The locus ceruleus contains mainly norepinephrine neurons and is considered to be a key brain center for anxiety, arousal, fear, and vigilance. Norepinephrine released from the locus ceruleus affects other parts of the brain (namely the nucleus accumbens), which can then lead to more feelings of anxiety and panic as well as an increased sense of energy. The locus ceruleus may be upregulated in addictive states as well.

Addictions, Stress, Anxiety, and Insomnia

Glycine, because of its effects on this one area of the brain, can be used as an adjunctive treatment in several conditions. In people suffering from drug and alcohol dependency, it is thought that this area of the brain is periodically upregulated, leading to excessive norepinephrine release. People who become dependent on substances may use drugs or alcohol to satisfy the cravings created by an upregulated locus ceruleus. Other conditions in

Potentials for Other Amino Acids

The realm of amino acids and their treatments is of course not limited to those included in this paper. We encourage readers to investigate the many other amino acids available for treating a multitude of other medical conditions. Some of these include:

- *Alanine*—blood-sugar regulation
- *Branched chain amino acids (leucine, isoleucine, and valine)*—postoperative conditions, liver disease
- *Citrulline*—cholesterol and cancer; as a precursor to nitric oxide
- *Cysteine and glutathione*—as detoxification and antiaging agents
- *Histidine*—for arthritis
- *Lysine*—herpes and osteoporosis
- *Methionine*—cystitis and allergy
- *Ornithine*—as a potential growth-hormone imitator
- *Phenylalanine*—pain relief
- *Proline and hydroxyproline*—telopeptides, collagen, and aging
- *Serine*—psychiatric disorders, mood, and memory
- *Threonine*—immune system function, precursor to phosphatidyl serine
- *Tyrosine*—antidepressant
- *Tryptophan and melatonin*—anxiety, depression, and sleep disorders
- *Taurine*—antiseizure.

which glycine can be useful for downregulation of the locus ceruleus are panic disorders, nervous tension, anxiety, substance withdrawal, and insomnia (which is marked by awakening with anxiety).

Glycine also interacts in an inhibitory action with motor neurons in the spinal cord and can have a calming effect on muscle spasms, muscle twitching, guarding, and rigidity that results from excessive spinal reflex activity. Glycine can inhibit spasming associated with the urinary and reproductive systems as well.¹⁹

Schizophrenia

Glycine works as an agonist at another type of receptor site in the central nervous system: the N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are associated with memory and learning²⁰ and are thought to play a role in both the negative and positive symptoms of schizophrenia.²¹

Schizophrenia is thought to be associated with underactivity of glutamatergic receptors, especially the NMDA type. In schizophrenic patients, those that have demonstrated resistance to therapy using singular antipsychotic medications have experienced a decreased amount of schizophrenic symptoms with glycine treatment.²² Glycine was also shown to reduce depressive and cognitive symptoms in these patients.

In the study with the patients who were resistant to singular antipsychotics, the investigators noted that the greatest symptomatic improvements were made in subjects with the lowest baseline serum glycine amounts.

However, another investigation revealed that, when used with the atypical neuroleptic drug clozapine, glycine demonstrated no *statistically* significant change in symptoms or cognitive functioning,²³ while another study showed that patients treated with clozapine without glycine (in comparison to another group treated with both) fared better in terms of symptom reduction.²⁴ These investigators concluded, based on their findings, that glycine may interfere with atypical neuroleptics such as clozapine.

Dosing Review for 5 Amino Acids

Amino acid	Comments
Glutamine	<i>Gastrointestinal-related conditions:</i> Typical doses are 4 g, swished and swallowed (can be taken several times per day) <i>Immune function:</i> Most studies have shown benefit using doses from 3 to 6 g per day.
Glycine	Typical doses start at 4 g per day and are increased by 4 g per day
Dimethylglycine	Typical dose is 125 mg per day, with food
N-acetyl-carnitine	<i>Alzheimer's disease:</i> 1500–4000 mg, in divided doses, per day <i>Age-related memory impairment:</i> 1500–2000 mg per day <i>Stroke recovery:</i> 1500 mg per day <i>Age-related depression:</i> 1500–3000 mg, in divided doses, per day.
Arginine	Typical doses range from 3 to 20 g per day, in divided doses

NOTES: There are no Recommended Daily Allowances for any of the amino acids in this chart.

See Conclusions and Caveats section in the text for information about the importance of vitamin B₆.

Dimethylglycine

Dimethylglycine (DMG) is a methylated form of the amino acid glycine. DMG is produced in the body, but exists for only a few seconds before undergoing conversion. (It is formed from betaine as homocysteine is methylated).²⁵ Acting as a methyl group donor, DMG has a reputation for benefiting children with autism, who have symptomatic improvement within days of taking the supplement.

Other research shows that DMG also has an immune-enhancing effect. Both humoral and cell-mediated immune responses are increased with DMG supplementation.²⁶ DMG is absorbed in the small intestine and metabolized in the liver to monomethylglycine or "sarcosine," which, in turn, is converted into glycine. DMG has been shown to have anticonvulsant effects in patients with mixed complex partial and grand mal seizures.²⁷ Some research has investigated DMG for improvement of oxygen utilization, liver function, and athletic performance.²⁸

N-Acetyl-Carnitine

Derived from the amino acid carnitine, N-acetyl-carnitine is an ester form of carnitine; it is sometimes referred to as acetyl-L-carnitine and is structurally similar to the neurotransmitter acetylcholine. Formed in small amounts inside the mitochondria, N-acetyl-carnitine is a precursor to the molecule acetyl coenzyme A (which is, in turn, a structural segment of acetylcholine²⁹) and is thought to enhance the activity of the cholinergic nervous system. In addition, N-acetyl-carnitine assists transportation of acetyl groups into the mitochondria and enhances production and release of the neurotransmitter acetylcholine.³⁰

Neurologic Function

N-acetyl-carnitine is also thought to have neuroprotective effects, assisting the serotonin neurotransmitter pathways, enhancing transmission of nerve impulses in the brain, and decreasing loss of age-related glucocorticoid receptors in the hippocampus. In conditions of compromised cerebrovascular blood flow, N-acetyl-carnitine may increase blood flow to the brain in patients with cerebrovascular disease.³¹

N-acetyl-carnitine is also beneficial for people with vascular dementia and those who are recovering from strokes.³² This amino acid has improved cerebral blood flow in people with chronic brain ischemia after only one dose.³³ The supplement can improve memory and visual-spatial orientation skills in individuals with cognitive impairment who are recovering from alcohol dependency.³⁴

Similarly, N-acetyl-carnitine may improve cognitive function and memory in people with age-related cognitive decline and memory impairment.³⁵ Much research has been done, using this compound, to help people with Alzheimer's disease, which is marked by a significant decrease in acetylcholine and cholinergic neurons.³⁶

AIDS, Energy, Fertility

Other uses of this amino acid include impeding the decline of CD4 lymphocytes in patients with acquired immunodeficiency syndrome (AIDS).³⁷ N-acetyl-carnitine is also used for treating HIV medication-related neuropathy.³⁸ Similar to carnitine, N-acetyl-carnitine improves energy production and is included in formulas designed for weight loss, as this compound assists in the transport of long-chain fatty acids into the mitochondria, where they are used for energy production.³⁶ N-acetyl-carnitine is found in the seminal fluid and sperm and is used to improve sperm motility; this compound has been found to be low in infertile and low-motility sperm samples.³⁹

Arginine

Arginine is a conditionally essential amino acid because it can be synthesized from the amino acids glutamine, glutamate, and proline. Despite this, dietary intake remains the preferred means of obtaining this amino acid because the rate of arginine synthesis in the body is not altered in response to depletion or low supplies.⁴¹ Arginine exerts many positive effects in the body, not all of which are covered here. One area where arginine has significant use and effect is on the endocrine system, specifically adrenal and pituitary function. Arginine is well known for its ability to stimulate catecholamine release, insulin and glucagon, prolactin, and growth hormone.⁴¹ The mechanism of action behind these effects is not well-understood at present.

Immune Function

A potent immune system modulator, arginine is useful for treating suboptimal immune responses and can reduce the occurrence of postsurgical infections. Supplemental arginine can decrease the amount of cell-adhesion molecules (useful for preventing viral and bacterial entry) and lowers proinflammatory

cytokines; arginine's effects on these molecules are thought to alter the balance of cytokines positively. In one study, arginine (30 g per day, for 3 days) upregulated natural killer-cell activity, lymphocyte reactivity, and lymphokine activation of natural killer cells in patients with breast cancer.⁴² Conversely, arginine may promote tumor growth by providing a source of nitrogen.⁴³

Cardiovascular System

Arginine is best known for its effects on the cardiovascular system. It is a precursor for nitric oxide synthase, which converts arginine into nitric oxide (NO) in the vascular endothelial cells. NO is also known as endothelium-derived relaxation factor that causes vasodilation in the vasculature. Many of arginine's effects are thought to be the result of this effect. NO itself is a vastly important molecule in several vascular-related conditions including maintenance of blood pressure⁴⁴ and proper myocardial function.⁴⁵

Angina Pectoris

Arginine has been shown to reduce the symptoms of angina pectoris and increase exercise tolerance and improve quality of life in people with various grades (class II, III, and IV) of the condition.⁴⁶ In patients with class IV angina pectoris, who do not benefit from standard antianginal medications, arginine was thought to provide a significant clinical benefit.⁴⁷ Not all investigations of arginine and angina pectoris have shown a benefit, however.

Congestive Heart Failure

Patients with congestive heart failure (CHF) experience reduced peripheral blood flow at rest and exercise. NO derived from arginine can assist regulation of blood flow in these patients. In a double-blinded trial, investigators demonstrated a significant improvement in blood flow, arterial compliance, and functional status in patients who received doses ranging from 5.6 to 12.6 g of arginine, 3 times a day, for 6 weeks, over patients on placebo.⁴⁸ Another study demonstrated positive effects on kidney function (important in CHF) as evidenced by increased glomerular filtration rate, creatinine clearance, and elimination of sodium and water following saline loading.⁴⁹

Other Uses

Arginine has demonstrated usefulness for addressing several other vascular-related conditions, including erectile dysfunction,⁵⁰ peripheral artery disease,⁵¹ and renal transplants.⁵² Other conditions include AIDS-related wasting syndrome,⁵³ interstitial cystitis,⁵⁴ necrotizing enterocolitis,⁵⁵ and postsurgical recovery.⁵⁶

Conclusions and Caveats

When using amino acids for treatment, a highly important dietary consideration should be kept in mind. Vitamin B₆ (pyridoxine) is necessary for the metabolism of amino acids, lipids, and carbohydrates in the body. Converted into the coenzymes pyridoxal phosphate and pyridoxamine phosphate, vitamin B₆ is involved in the function of approximately 60 enzyme systems including transamination of amino acids, the

synthesis of gamma-aminobutyric acid in the brain, and the conversion of tryptophan to niacin. Vitamin B₆ plays a critical role in healthy brain function because of the vitamin's role in producing amino-acid based neurotransmitters (serotonin, dopamine, melatonin, epinephrine, and norepinephrine). Finally, vitamin B₆ is needed for the metabolism of the amino acid homocysteine, which is an independent risk factor for cardiovascular disease.

More amino acids than the ones covered in this article have potential for addressing a range of conditions either for prevention or treatment (see box entitled Potentials for Other Amino Acids). □

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