



L-Tryptophan

Introduction

L-tryptophan (tryptophan; Trp) is a large neutral amino acid essential to human metabolism because it is the metabolic precursor of serotonin (a neurotransmitter), melatonin (a neurohormone), and niacin (vitamin B3).

As a component of dietary protein, tryptophan is particularly plentiful in chocolate, oats, bananas, dried dates, milk, cottage cheese, meat, fish, turkey, and peanuts. Approximately 300 mg Trp is available in three ounces of turkey, lamb, beef, tuna, or peanuts.¹ Relative to other amino acids, small amounts are needed to have a therapeutic effect, which is fortunate because Trp is the least abundant amino acid in the diet.²

In 1989, the importation of L-tryptophan was banned in the United States after cases of a deadly autoimmune illness called eosinophilia-myalgia syndrome were traced to an improperly-prepared batch of tryptophan.³ Although the tryptophan was isolated to a single Japanese factory that allowed a toxic bacterial metabolite through the purification process, the ban was maintained and Trp availability was limited to the prescription drug (Tryptan), infant formulas, and enteral feeding products. Since 1994 tryptophan has been available and marketed as a dietary supplement in the United States, while imported product remains limited by special regulations.

Pharmacokinetics

The most investigated aspect of tryptophan metabolism is the serotonin pathway that includes the subsequent creation of melatonin. Tryptophan hydroxylase is the rate-limiting enzyme for serotonin production and involves the conversion of Trp to 5-hydroxytryptophan (5-HTP). This enzyme can be inhibited by stress, insulin resistance, magnesium or vitamin B6 deficiency, or increasing age.⁴ The decarboxylation of 5-HTP to serotonin is dependent on the presence of the active form of vitamin B6, pyridoxal 5'-phosphate, while the further conversion to melatonin necessitates S-adenosyl-L-methionine (SAMe).

Tryptophan and 5-HTP penetrate the blood-brain barrier, although tryptophan requires active transport and competes for the same receptors with other neutral amino acids – tyrosine, phenylalanine, valine, leucine, and isoleucine.^{5,6} In fact, the best predictor of a given meal's effect on brain tryptophan and serotonin levels is the serum ratio of Trp to the pool of large neutral amino acids.⁷ More clinically relevant, however, serotonin levels are enhanced by carbohydrate ingestion as insulin release accelerates the serum removal of competing valine, leucine, and isoleucine. Similarly, a higher percentage of protein in the diet slows serotonin elevation.^{5,8}

Although tryptophan can be found free in the serum, most is bound to albumin. Nonesterified fatty acids out-compete Trp for albumin's common binding site,⁹ while displacement from albumin is also associated with the release of free fatty acids during exercise.¹⁰

The urinary metabolites of tryptophan include 3-hydroxykynurenine, xanthurenic acid, and kynurenine. Serum kynurenine, however, is metabolized into niacin (vitamin B3). This conversion is inefficient since 60 mg of tryptophan are required to synthesize 1 mg of niacin, which also depletes stores of the vitamin cofactors B1, B2, and B6.^{11,12}

Mechanism of Action

Tryptophan's primary mechanism of action is its role as the metabolic precursor of the neurotransmitter serotonin. Other neurotransmitters and central nervous system (CNS) chemicals, such as melatonin, dopamine, norepinephrine, and beta-endorphin, have also been shown to increase following oral administration of tryptophan.¹³⁻¹⁶

There is limited data linking tryptophan's modulation of the endocrine system. Tryptophan's effects on cortisol levels have been inconsistent.^{17,18} Although intravenous tryptophan stimulates secretion of prolactin and growth hormone,^{19,20} such an association has not been tested with oral dosing.

Clinical Indications

Premenstrual Syndrome (PMS)

A dose of 6 g tryptophan has been found to significantly ($p=0.004$) decrease mood swings, tension, and irritability in women with premenstrual

dysphoria. Three consecutive cycles, from ovulation to the third day of menstruation, were assessed using the Visual Analog Mood Scales.²¹ Tryptophan's role in PMS may be attributed to the increased activation of tryptophan catabolism to kynurenine during the luteal phase of the menstrual cycle.²²

Seasonal Affective Disorder (SAD)

In the case of SAD, tryptophan has shown benefit in non-responders to light therapy. Four weeks of treatment with Trp (2 g twice daily, increased to 2 g three times daily if initially no response) was compared to light therapy (10,000 lux x 30 min daily in the morning). At the end of seven weeks, similar significant responses were noted in both groups ($p=0.014$ in Trp group). However, when light therapy was discontinued patients quickly relapsed; whereas, patients on tryptophan had a slower relapse rate.²³ Similar results were demonstrated in 13 SAD patients treated with light therapy or tryptophan.²⁴

Sleep Disorders

Tryptophan has been researched for sleep disorders for 30 years. Improvement of sleep latency has been noted,^{25,26} even at doses as low as 1 g;²⁷ increased stage IV sleep has been noted at even lower doses – 250 mg tryptophan.²⁷ Significant improvement in obstructive sleep apnea, but not central sleep apnea, has been noted at doses of 2.5 g at bedtime, with those experiencing the most severe apnea demonstrating the best response.²⁸

While many sedative medications have opioid-like effects, L-tryptophan administration does not limit cognitive performance or inhibit arousal from sleep.^{25,29}

Depression and Other Mental Disorders

The tryptophan metabolite, 5-HTP, has shown significant clinical response for depression in 2-4 weeks, at doses of 50-300 mg three times daily.³⁰⁻³⁶ Although reduced levels of serum Trp have been linked to some forms of depression, depression was not relieved with intravenous tryptophan.³⁷ Numerous studies, however, have found tryptophan depletion produced depressive relapse and even initiation of depressive symptoms in healthy subjects.³⁸⁻⁴²

Tryptophan depletion has also been shown to promote relapse of bulimia⁴³ and schizophrenia,⁴⁴ indicating the pivotal requirements for tryptophan in mental disorders other than depression.

Tryptophan supplementation should be avoided in depression with reversed diurnal variation (worse in the evening), which commonly presents with an elevated ratio of tryptophan to large neutral amino acids and poor response to serotonergic antidepressants.⁴⁵

Smoking

Tryptophan (50 mg/kg/day) has been used as an adjunct therapy for smoking cessation. During a two-week study, tryptophan-treated subjects experienced fewer nicotine withdrawal symptoms and were able to abstain or smoke fewer cigarettes than controls.⁴⁶

Diagnosis of a Vitamin B6 Deficiency

The Tryptophan Load Test is a lab evaluation of vitamin B6 status. Elevated urinary xanthurenic acid (>50 mg/24 hr) after 2 g Trp is commonly viewed as a sign of a deficiency of vitamin B6,⁴⁷ although it can be falsely elevated in pregnancy⁴⁸ and in women using oral contraceptives.⁴⁹ Xanthurenic acid elevation has also been associated with cataract formation.⁵⁰

Drug-Nutrient Interactions

Case reports of serotonin syndrome have noted a connection between tryptophan used concomitantly with monoamine oxidase inhibitors.^{51,52} This syndrome is characterized by agitation, confusion, delirium, tachycardia, diaphoresis, and blood pressure fluctuations. Although no reports have been published, it is possible that tryptophan, when taken in combination with a selective serotonin reuptake inhibitor (SSRI) such as Prozac®, Paxil®, or Zoloft®, may also precipitate serotonin syndrome.

Side Effects and Toxicity

Potential side effects at high doses (100 mg/kg/day, i.e., 7 g/150 lbs) include gastric irritation, vomiting, and head twitching.¹

Warnings and Contraindications

Patients with liver cirrhosis should avoid tryptophan supplementation. Cirrhotics present with reduced activity of tryptophan pyrrolase (22%), with subsequent increased free tryptophan and half-life, with decreased clearance.⁵³

The effects of supplemental tryptophan during pregnancy are scarce. One study monitored fetal breathing activity via ultrasound over a 3.5-hour period and noted alteration in fetal breathing activity after maternal Trp loading (1 g) was less than observed after glucose load (100 g).⁵⁴ This, however, was a low dose of tryptophan. Further safety studies are warranted before use during pregnancy can be recommended.

Dosage

Evening oral doses of tryptophan as low as 250 mg have been shown to improve sleep quality, although the typical dosage range for sleep disorders and depression is 1-3 g daily. Safe and effective dosages for other disorders range from 0.5-4 g daily, while potentially higher doses (50 mg/kg/day) have been used short term as a smoking cessation intervention.

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