L-Tryptophan

DESCRIPTION

L-tryptophan is one of the eight essential amino acids for humans (10 for children). It is the least abundant essential amino acid. An essential amino acid is an amino acid that the body can not make, or if it can, it does not make it in sufficient amounts for all of its biological needs (for example, L-histidine and L-arginine for children). L-tryptophan is a protein amino acid, meaning that it is a building block of proteins. L-tryptophan also has other important functions. It is the precursor of the neurotransmitter serotonin, the pineal gland hormone melatonin (see Melatonin), the possible neuroprotectant kynurenic acid, vitamin B_3 (niacin or nicotinic acid and niacinamide or nicotinamide), and the coenzymes NADH (nicotinamide adenine dinucleotide) and NADPH (nicotinamide adenine dinucleotide phosphate).

A deficiency of niacin and/or L-tryptophan causes pellagra, which is characterized by the three Ds of dermatitis, diarrhea and dementia, and, if untreated for some time, a fourth D, death. Pellagra is a vitamin B_3 deficiency disease caused by dietary lack of niacin and protein, especially proteins containing the essential amino acid L-tryptophan. Because L-tryptophan can be converted into niacin, foods with L-tryptophan but without niacin, such as milk, prevent pellagra. However, if dietary L-tryptophan is diverted into the production of protein, niacin deficiency may still exist, leading to pellagra.

By the end of the 1980s, some millions of people, mainly women and mainly in the United States, were using supplemental L-tryptophan for a variety of reasons—premenstrual syndrome (PMS), sleep disorders, anxiety, depression, fibromyalgia, seasonal affective disorder (SAD) and chronic pain syndromes. Supplemental L-tryptophan was also used as an adjunct in the treatment of cocaine, amphetamine, alcohol and other drug abuse and for jet lag. In the context of the intensive care unit, some physicians used it as a sedative to help relax their intensive care unit patients with a substance that was less likely to suppress their respiration than a pharmaceutical sedative might. The physicians thought that this was particularly useful for those patients who had compromised respiration to begin with.

In fact, there were even some clinical studies that appeared to support some of the above uses of L-tryptophan.

In the fall of 1989, L-tryptophan supplementation was to see its darkest days. In October 1989, Dr. Philip Herzman and his colleagues in New Mexico met to compare notes on three female patients with unusual clinical presentations involving myalgia (muscle pain), weakness, oral ulcers, abdominal pain, skin rash and a striking increase in eosinophils (a subset of white blood cells) in their blood. These physicians recognized that all three patients developed these symptoms after using supplemental L-tryptophan, and they thought that the supplemental L-tryptophan might have caused the problem. They reported the illnesses and their suspected association of the illnesses to supplemental L-tryptophan to the New Mexico Health and Environment Department and the CDC (Centers for Disease Control and Prevention). The New Mexico Health and Environmental Department discovered several similar cases, almost all of which involved supplemental L-tryptophan. As awareness of the problem grew—the CDC notified all state health departments about a health problem possibly due to ingestion of supplemental L-tryptophan—a number of cases were reported from other states. In November 1989, the CDC proposed the name of eosinophilia-myalgia syndrome, or EMS, for the disease, since all the presumptive cases had both eosinophilia (elevation of eosinophils in their blood) and severe myalgia (muscle pain). Since trichinosis also causes eosinophilia and myalgia, the initial CDC surveillance definition of an EMS case required serological testing or a muscle biopsy to rule

out trichinosis. However, since the clinical presentation of EMS was sufficiently distinct from trichinosis, the initial requirement of negative testing for trichinosis was dropped from the surveillance definition.

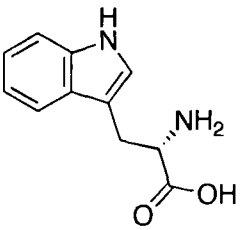
The association between use of supplemental L-tryptophan and EMS was a strong one and on November 11, 1989, the FDA issued a nationwide warning advising consumers to discontinue the use of L-tryptophan supplements and subsequently requested a nationwide recall of all L-tryptophan products sold over-the-counter. With the removal of L-tryptophan supplements from the marketplace, the number of reported new cases of EMS dropped rapidly. As of June 1993, 1,511 cases of EMS had been reported to the CDC, including 37 deaths. Although the preponderance of EMS cases came from the United States, 97 cases were reported from Germany, 24 from France, 16 from Canada, three each from Switzerland and Belgium, two each from the UK, and Japan and one each from Spain and Australia. In the United States, 84% of the cases were women and 97% non-Hispanic white, and the highest incidence of EMS cases was in the Western states. In terms of risk factors, the number one risk factor for EMS was the use of L-tryptophan supplements. The dose of supplemental L-tryptophan and the age of the user were also considered risk factors for EMS. Older users of L-tryptophan were more likely to develop EMS than younger users and the risk of developing EMS increased with larger doses of L-tryptophan. A 50% attack rate was demonstrated in those who ingested more than four grams of L-tryptophan on a regular basis, suggesting that the EMS agent was a toxicant.

The hunt for possible toxicants and contaminants in the suspected L-tryptophan supplements that could be identified as causing EMS immediately began, but, although some suspects were identified, none was positively identified that could have caused EMS.

In 1991, the FDA banned L-tryptophan supplements from sale in the U.S. In 2001, the FDA loosened the restriction on the marketing of L-tryptophan supplements, but did ban its importation except under certain circumstances. As of May 2, 2005, the FDA completely cancelled the import ban alert for L-tryptophan. Following this, L-tryptophan supplements began again appearing on the nutritional supplement marketplace, including in health food stores, compounding pharmacies and over the Internet, where they continue to be found.

L-tryptophan is chemically described as (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoic acid.

It is also known as (*S*)-alpha-amino-1*H*-indole-3-propanoic acid and 2-amino-3-indolylpropanoic acid. It is abbreviated as Trp or by its one-letter designation W. Its empirical formula is $C_{11}H_{12}N2O_2$, its molecular weight is 204.22 and its CAS Registry Number is 73-23-3. The minimum daily requirement for L-tryptophan is said to be 0.25 grams daily for males and 0.15 grams for females. The average Western diet contains about one to three grams daily. L-tryptophan is represented by the following chemical structure.



L-Tryptophan

ACTIONS AND PHARMACOLOGY

ACTIONS

L-tryptophan may have antidepressant activity, activity against premenstrual syndrome (PMS) and sleep-promoting activity.

MECHANISM OF ACTION

Antidepressant activity: A Cochrane Collaboration meta-analysis concluded that although a number of studies were performed to determine if L-tryptophan and 5-hydroxytryptophan (5-HT, see 5-Hydroxytryptophan) possessed antidepressant activity, only a few were of sufficient quality to be reliable. However, those few did suggest that both L-tryptophan and 5-hydroxytryptophan were better than placebo at alleviating depression. The authors also stated that "further studies are needed to evaluate the efficacy and safety of 5-HT and tryptophan before their widespread use can be recommended." The possible antidepressant effect is accounted for by the conversion of L-tryptophan and 5-hydroxytryptophan to the neurotransmitter serotonin.

In a double-bind placebo-controlled trial of L-tryptophan combined with the selective serotonin reuptake inhibitor (SSRI) fluoxetine, it was found that combining 20 milligrams of fluoxetine with two to four grams of L-tryptophan daily for a group diagnosed with major depressive disorder produced a more rapid antidepressant effect when compared with those patients who just used fluoxetine alone. The tryptophan group also seemed to have a protective effect on slow-wave sleep. The four gram per day dose of L-tryptophan, but not the two gram per day dose, produced daytime drowsiness. Again, the mechanism of action of the L-tryptophan was most likely due to its conversion to the neurotransmitter serotonin in the brain.

The mechanism of the possible antidepressant activity of L-tryptophan is accounted for by its conversion to the neurotransmitter serotonin, which plays a central role in the affective state. Antidepressants may work by either binding to one or more of the family of serotonin 5-HT receptors (5-

HT1—5-HT7) or by inhibiting the reuptake of serotonin. The tricyclic antidepressants may work, in part, by binding to the serotonin 5-HT6 receptor, a member of the G protein superfamily, which is positively coupled to an adenylate cyclase second-messenger system. The selective serotonin reuptake inhibitors (SSRIs) selectively inhibit the reuptake of serotonin.

Anti-premenstrual syndrome (PMS) activity: Prior to the recall of L-tryptophan in 1989, L-tryptophan supplementation was used by many women for relief of PMS symptoms. A number of studies lent some support to this use. One placebo-controlled clinical trial of L-tryptophan in PMS showed that increasing serotonin levels during the late luteal phase of the menstrual cycle via administration of L-tryptophan had a beneficial effect in patients with PMS.

Sleep-promoting activity: Over the course of more than 40 years, a number of studies have suggested that L-tryptophan reduces sleep latency, produces an increase in rated subjective sleepiness and a decrease in total wakefulness and/or increase in sleep time. The best results have been in those with mild insomnia. It is thought that the sleep-promoting effect of L-tryptophan is accounted for by its conversion to the neurohormone melatonin.

A recent study determined the effect of L-tryptophan intake on age-related changes in the activity-rest circadian rhythms and c-fos expression of ring doves with aging. C-fos is a cellular proto-oncogene. Neuroscientists measure expression of c-fos as an indirect marker of neuronal activity because c-fos is often expressed when neurons fire action potentials. The suprachiasmatic nucleus (SCN) is a bilateral region of the brain, located in the hypothalamus, which is responsible for controlling endogenous circadian rhythms. The hormonal and neuronal activities it generates regulate many different bodily functions over a 24-hour period. Both L-tryptophan and melatonin, a metabolite of L-tryptophan made in the pineal gland, reduced the nocturnal activity of all ring doves. However, only the highest doses were effective in the old ring doves. Sleep parameters, calculated from the activity data, indicated worsened sleep quality in old animals, but it was improved with the treatments. In addition, the expression of c-fos in the suprachiasmatic nucleus was reduced after both treatments.

The suprachiasmatic nucleus appears to be the target for the observed nocturnal effects of L-tryptophan and melatonin. Further, this supports the use of L-tryptophan to reverse the disturbances of the circadian activity-rest cycle related with aging.

PHARMACOKINETICS

Following ingestion, L-tryptophan is absorbed from the small intestine by a sodium-dependent active transport process. L-tryptophan is transported from the small intestine to the liver via the portal circulation. In the liver, L-tryptophan is involved in a number of biochemical reactions, including protein synthesis and oxidative catabolic reactions. L-tryptophan that is not metabolized in the liver is distributed via the systemic circulation to the various organs and tissues of the body where it undergoes metabolic reactions similar to those that take place in the liver. L-tryptophan can cross the blood-brain barrier via an active transport mechanism. L-tryptophan is the precursor of serotonin (5-hydroxytyramine, or 5-HT), melatonin, kynurenine, nicotinic acid and nicotinamide adenine dinucleotide (NAD). Within the CNS, greater than 95% of L-tryptophan is catabolized through the kynurenine (KYN) pathway, resulting, among other things, in the production of neuroactive intermediates, which can be neurotoxic or neuroprotective.

L-tryptophan is converted into serotonin in two steps, the first via the enzyme tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP) and the second via vitamin B_6-dependent L-aromatic amino acid decarboxylase to serotonin, or 5-HT. Serotonin is subsequently metabolized to 5-hydroxyindole acetaldehyde, which is rapidly metabolized to 5-hydroxyindoleacetic acid (5-HIAA) via the enzyme monoamine oxidase (MAO).

The uptake of the serotonin precursor L-tryptophan into the brain depends on nutrients that influence the availability of L-tryptophan by changing the ratio of plasma L-tryptophan to the sum of the other large neutral amino acids (LNAAs). The LNAAs are L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine. The ratio of L-tryptophan to the LNAAs is increased by foods such as carbohydrates and the whey protein alpha-lactalbumin. An increase in the plasma L-tryptophan to LNAA ratio is considered to be an indirect indication of increased availability of brain serotonin.

L-tryptophan is converted into melatonin in four steps—the first via the enzyme tryptophan hydroxylase to 5-hydroxytryptophan and the second via vitamin B_6-dependent L-aromatic amino acid decarboxylase to serotonin. Serotonin is then metabolized to N-acetylserotonin via serotonin N-acetyltransferase and finally to melatonin via the enzyme hydroxyindole-O-methyltransferase, using S-adenosylmethionine (SAMe) as the methyl donor.

L-tryptophan is converted into niacin in six steps: L-tryptophan to kynurenine via tryptophan pyrrolase, kynurenine to 3-hydroxykynurenine, 3-hydroxykynurenine to 3-hydroxyanthranlic acid, 3-hydroxyanthranilic acid to carboxymuconic aldehyde intermediate, carboxymuconic aldehyde intermediate to quinolinic acid and quinolinic acid to nicotinic acid. Carboxymuconic aldehyde intermediate is also converted to picolinic acid.

The kynurenine pathway is the major pathway of L-tryptophan catabolism. It is also responsible for the biosynthesis of the coenzyme nicotinamide adenine dinucleotide, or NAD. 95% of L-tryptophan ingested from the diet is metabolized via the kynurenine pathway, while only a small amount is converted into 5-hydroxytryptamine, or serotonin.

There has been increasing interest in the kynurenine pathway over the last few years for a several reasons. A number of important physiological functions have been associated with this pathway, including behavior and thermoregulation; it is implicated in a number of different neurological disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, cognitive decline, cerebral ischemia, convulsive disorders, HIV/AIDS dementia and schizophrenia. The kynurenine pathway possesses neuroactive metabolites with different biological properties, including prooxidant and antioxidant activities, and proinflammatory and anti-inflammatory activities. It also appears to be involved in neuroprotection, immune regulation and tumor inhibition. Clearly, this is an extremely complex pathway with a wide range of effects, both negative and positive, and much study of it is needed and certainly warranted.

In the liver, the indole ring of L-tryptophan is oxidatively excised via the enzyme tryptophan 2,3-dioxygenase (TDO) to produce N-formyl kynurenine. In the brain and peripheral tissues, the enzyme responsible for this reaction is indolamine 2,3-dioxygenase (IDO), which requires superoxide anions for its activity. Therefore, IDO requires enzymatic systems that generate oxidative species. IDO is inhibited by superoxide dismutase (SOD) and nitric oxide (NO). Significantly, IDO may itself act as an antioxidant. The next step in the kynurenine pathway is the degradation of N-formyl kynurenine to L-kynurenine via the enzyme kynurenine formamidase. L-kynurenine can serve as a substrate for the enzyme kynurenase, which converts it to anthranilic acid, kynurenine 3-hydroxylase, which converts it to 3-hydroxykynurenine and kynurenine aminotranferases, which are responsible for the irreversible transamination of L-kynurenine to kynurenic acid.

The kynurenine pathway then proceeds to the formation of quinolinic acid via a few steps, starting with the hydroxylation of L-kynurenine to 3-hydroxykynurenine catalyzed by kynurenine 3-hydroxylase, followed by the conversion of 3-hydroxykynurenine to 3-hydroxyanthranilic acid. 3-hydroxyanthranilate dioxygenase then opens the ring of 3-hydroxyanthranilic acid to produce 2-amino-3-carboxymuconate-semialdehyde, which is rapidly transformed into quinolinic acid. Quinolinic acid is metabolized to nicotinic acid dinucleotide (NAD) via quinolate phosphoribosyl tranferase.

Urinary metabolites of tryptophan include 3-hydroxykynurenine, xanthurenic acid and 5-hydroxyindoleacetic acid (5-HIAA). The major metabolite of L-tryptophan found in the feces is skatole (3-methylindloe).

INDICATIONS AND USAGE

L-tryptophan, an essential amino acid and precursor of the neurotransmitter serotonin, though previously banned by the FDA, is again available as a nutritional supplement. Once possibly associated with a deadly autoimmune disorder called eosinophilia-myalgia syndrome (EMS), the FDA banned most of it from sale in the United States in 1991. The possible association with EMS, however, was never conclusively proved, and some researchers questioned the data linking the amino acid with EMS. Subsequently, in 2001, the FDA relaxed restrictions on marketing the substance (though at the time it continued to prohibit its importations from other countries). It did so, however, with reservations at the time, stating: "Based on the scientific evidence that is available at the present time, we cannot determine with certainty that the occurrence of EMS in susceptible persons consuming L-tryptophan supplements derives from the content of L-tryptophan, an impurity contained in the L-tryptophan, or a combination of the two in association with other, as yet unknown, external factors." As of May 2, 2005, the FDA completely cancelled the import alert.

Claims for L-tryptophan (found, for example, in meats, dairy products, various seeds, some grains, bananas, mangoes, dried dates, spirulina, some nuts and in protein-based foods generally), include antidepressant, sedative, hypnotic, anti-insomnia effects. It is said to have mood-modulating properties capable of ameliorating some of the symptoms of premenstrual syndrome and seasonal affective disorder. It has also been suggested that it might be helpful in more serious mental disturbances, including schizophrenia and bipolar disorder, and that it could have some ability to attenuate amphetamine abuse. It has also been claimed that it has anti-inflammatory effects.

RESEARCH SUMMARY

When a 1989 EMS outbreak resulting in 37 deaths and some 1,500 cases of permanent disability was linked by some to consumption of L-tryptophan supplements, the FDA soon acted to largely restrict the marketing and importation of the amino acid. Some claimed that there was evidence that the tryptophan that caused the problem was produced by one Japanese manufacturer. Additionally, a group of researchers reported that they found an impurity in the tryptophan produced by that manufacturer and they concluded that this was the most likely cause of the EMS outbreak, not the tryptophan itself. Further confounding the situation, however, were other reports that the problem could not conclusively be linked to the Japanese manufacturer and that EMS

had been associated with use of L-tryptophan both prior to and after the 1989 incident. Some others reported that excessive use of the amino acid, rather than any contaminant, might be the culprit, arguing that excess use results in metabolites that lead to impaired histamine metabolism, compromised histamine degradation and excessive histamine activity, which, in turn, they claim, can contribute to or cause EMS. However, none of that was ever proved. Hence the FDA eventually relaxed its restrictions on the marketing and importation of the amino acid.

As a number of researchers have noted over the years, L-tryptophan, as the precursor to serotonin synthesis, is a plausible candidate as a "natural" antidepressant. It is, in fact, licensed as an approved antidepressant in several countries. Generally, however, its efficacy as an antidepressant has been demonstrated in an adjunctive role with other established antidepressants, notably monoamine oxidative inhibitors. Evidence for its ability to combat depression on its own is not as clearly established. Clinical studies to date involving L-tryptophan and 5-hydroxytryptophan (5-HTP), which derives from the amino acid and crosses the blood-brain barrier and is converted to serotonin in the dopaminergic and serotonergic neurons, have yielded mixed results with respect to depression. Given its availability in the neurons just mentioned, it would be expected to have an antidepressant effect in some individuals and, in fact, it does in some studies, does not in some others and has a weak effect in still others. Some studies have found evidence that convinced their authors that the amino acid has effects similar to widely used serotonergic antidepressants.

A review of the literature recently led another group of researchers to conclude, however, that the data, so far, is inconclusive. Additionally, because the amino acid is not entirely clear of the EMS cloud, even at this late date, these authors clearly found the use of the substance unappealing. They did, however, state that large, well-designed, placebo-controlled studies are indicated. It should be mentioned in passing that one dated paper suggested that L-tryptophan might be more effective than lithium carbonate alone in the treatment of bipolar and schizophrenic patients. Follow-up is lacking and no conclusions can be drawn.

Claims that L-tryptophan might be a useful sleep aid, combating insomnia, are based on a few studies. One of these, dating back almost 40 years, described supplementation with the amino acid in seven patients suffering insomnia. It was claimed that they enjoyed increases in total sleep. Another dated paper, this one a review of several studies of the amino acid related to sleep, concluded that L-tryptophan has clinical hypnotic value. The studies upon which this review was based, however, were small and mostly poorly controlled, and the observed effects were often weak in terms of increased total sleep. Data were better in support of the claim of reduced sleep latency (time to fall asleep). The best effects, according to another reviewer, have been seen in normal (non-insomnia) subjects who have trouble initially falling asleep (latency) and in those with mild insomnia. Reduction in sleep latency has been achieved in these studies with, typically, doses of 1 to 15 grams of the amino acid. The sedative effect of L-tryptophan is attributed by some to either direct central serotonergic activation or to an indirect increase in melatonin levels or both.

L-tryptophan's relationship to melatonin (it is a melatonin precursor) has recently been studied on another front. Several studies have demonstrated that melatonin has some positive effects on animal models of ulcerative colitis, experimental pancreatitis and septic shock owing to its ability to favorably modulate a number of inflammatory factors. One recent study using a mouse contact hypersensitivity model reported a positive L-tryptophan effect reportedly achieved by promoting the production of the anti-inflammatory cytokine interleuken-10.

The possible role of L-tryptophan in the premenstrual syndrome (PMS) has been periodically investigated for some time. Some early research suggested a relationship between mood and other cyclical PMS changes and tryptophan metabolism. More recently, a pilot study of 13 patients diagnosed with late luteal phase dysphoric disorder (premenstrual depression) were treated with 6 grams daily of the amino acid with reported good results: significant amelioration of symptoms (depression, irritability, insomnia, carbohydrate craving). A prior study using only 1.5 grams of the amino acid daily had shown no positive result. Hence, these researchers stressed the need for the higher dosage used in their study. In a more rigorous follow-up study, the same group administered 6 grams of L-tryptophan to 37 patients with the same disorder and compared them with 34 matched controls who received placebo in a double-blind fashion. Treatments were administered for 17 days from time of ovulation to the third day of menstruation in each of three consecutive menstrual cycles. Again, the amino acid produced positive results based, it was said, upon its ability to increase serotonin synthesis during the late luteal phase of the menstrual cycle.

In a small open study, L-tryptophan was as effective as light therapy in vanquishing the symptoms of seasonal affective disorder (SAD). The amino acid was thought to be more durable than light in terms of treating SAD, in that relapse seemed to occur more slowly after withdrawal of L-tryptophan than it did after withdrawal of the light therapy.

Dietary tryptophan attenuated amphetamine self-administration in the rat in yet another study.

Given the various positive results achieved with this amino acid, research is clearly needed to definitively determine whether it is implicated in any way in EMS. If it is not, then clearly far more research is needed and warranted to follow up on these positive results in disparate, significant (and, in some cases, currently very difficult-to-treat) disorders. In this regard, it is worth noting that a prescription-only tryptophan product has been available since 1985 with, one group of researchers has stated, no cases of EMS reported.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Supplemental L-tryptophan is contraindicated in those hypersensitive to any component of an L-tryptophan-containing supplement.

PRECAUTIONS

Those who are interested in the use of L-tryptophan for any health condition should first discuss its use with his or her physician.

L-tryptophan should be avoided during or within 2 weeks after discontinuing the use of monoamine oxidase inhibitors (MAOIs).

Those with cataracts should be cautious in the use of L-tryptophan. Animal data suggest that photo-oxidation of L-tryptophan and some of its metabolites, particularly the metabolites found in the kynurenine pathway, may be involved in cataract formation. However, cataracts secondary to L-tryptophan use have not been reported in humans.

Those with bladder cancer should be cautious in the use of L-tryptophan. Some, but not all, animal studies have shown a relationship between L-tryptophan supplementation and bladder cancer. (There are no human reports of bladder cancer associated with the use of supplementary L-tryptophan.) It is thought that the risk for bladder cancer may be linked to a disorder of the metabolism of L-tryptophan that may be corrected by the administration of vitamin B_6.

Those with diabetes or a family history of diabetes should be cautious in the use of L-tryptophan. The L-tryptophan metabolite xanthurenic acid has been found to have a diabetogenic effect in animals. There are no human reports of diabetes associated with the use of supplemental L-tryptophan.

L-tryptophan should not be used concurrently with any antidepressant, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs). Concurrent use of L-tryptophan with any of these antidepressants may increase the risk of adverse reactions.

L-tryptophan should not be used concurrently with serotonin 5-HT1 receptor agonists, including naratriptan, sumatriptan, almotriptan, frovatriptan and zolmitriptan. Such use may increase the risk of adverse reactions.

L-tryptophan should be avoided by pregnant women and nursing mothers.

ADVERSE REACTIONS

Eosinophilia-myalgia syndrome (EMS). See Description and Research Summary above.

L-tryptophan in doses below five grams daily may cause daytime drowsiness, dizziness and dry mouth. Higher doses of L-tryptophan may cause nausea, anorexia and headache, as well as dizziness and daytime drowsiness.

INTERACTIONS

DRUGS

5-HT1 receptor agonists (naratriptan, sumatriptan, almotriptan, frovatriptan, zolmitriptan): Concurrent use of L-tryptophan with a 5-HT1 agonist may increase the risk of adverse reactions.

Monoamine oxidase inhibitors (MAOIs, eg, isocarboxazid, phenelzine sulfate, tranylcypromine): Concurrent use of L-tryptophan with an MAOI (type A) may increase the risk of adverse reactions.

Selective serotonin reuptake inhibitors (SSRIs, such as citalopram, escitalopram, fluvoxamine maleate, fluoxetine, paroxetine, sertraline, venlafaxine): Concurrent use of L-tryptophan with an SSRI may potentiate the antidepressant effect of the SSRI and may also increase the risk of adverse reactions.

Lithium: Clinical observations suggest the possibility that the combination of L-tryptophan and lithium may reduce the need for the higher, more toxic doses of lithium necessary to control bipolar affective disorders.

NUTRITIONAL SUPPLEMENTS

None known.

FOODS

Alpha-lactalbumin, carbohydrates, whey protein: May increase the brain availability of L-tryptophan.

HERBS

None known.

OVERDOSAGE

No reports in humans.

DOSAGE AND ADMINISTRATION

Those who wish to use L-tryptophan should only use the highest quality and purity grade L-tryptophan, preferably pharmaceutical grade and 99% to 100% pure, and should

make sure the L-tryptophan is manufactured by a trusted and respected company under the highest quality control conditions.

Dosage should be discussed with one's physician.

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L-Tyrosine

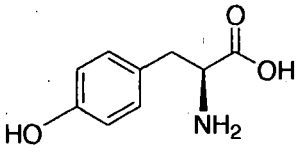
DESCRIPTION

L-tyrosine is a protein amino acid. It is classified as a conditionally essential amino acid.

Under most circumstances, the body can synthesize sufficient L-tyrosine, principally from L-phenylalanine, to meet its physiological demands. However, there are conditions where the body requires a dietary source of the amino acid for its physiological demands. For example, L-tyrosine is an essential amino acid for those with phenylketonuria. L-tyrosine is found in proteins of all life forms. Dietary sources of L-tyrosine are principally derived from animal and vegetable proteins. Vegetables and juices contain small amounts of the free amino acid. The free amino acid is also found in fermented foods such as yogurt and miso.

In addition to being involved in protein synthesis, L-tyrosine is a precursor for the synthesis of the catecholamines epinephrine, norepinephrine and dopamine, the thyroid hormones thyroxine and triiodothyronine, and the pigment melanin.

L-tyrosine is also known as beta- (para-hydroxyphenyl) alanine, alpha-amino-para-hydroxyhydrocinnamic acid and *(S)*- alpha-amino-4-hydroxybenzenepropanoic acid. It is abbreviated as either Tyr of by its one-letter abbreviation Y. The molecular formula of L-tyrosine is $C_9H_{10}NO_3$, and its molecular weight is 181.19 daltons. L-tyrosine is an aromatic amino acid with the following structural formula:



L-tyrosine

ACTIONS AND PHARMACOLOGY

ACTIONS

L-tyrosine has putative antidepressant activity.

MECHANISM OF ACTION

The mechanism of L-tyrosine's putative antidepressant activity may be accounted for by the precursor role of L-tyrosine in the synthesis of the neurotransmitters norepinephrine and dopamine. Elevated brain norepinephrine and dopamine levels are thought to be associated with antidepressant effects.

PHARMACOKINETICS

Following ingestion, L-tyrosine is absorbed from the small intestine by a sodium-dependent active transport process. L-tyrosine is transported from the small intestine to the liver via the portal circulation. In the liver, L-tyrosine is involved in a number of biochemical reactions, including protein synthesis and oxidative catabolic reactions. L-tyrosine that is not metabolized in the liver is distributed via the systemic circulation to the various tissues of the body.

INDICATIONS AND USAGE

Results are mixed, but largely negative, with respect to claims that tyrosine is an effective antidepressant. Claims that it can alleviate some of the mental and physical