

ON THE COVER

Why Aging People Become Depressed, Fatigued, and Overweight

By William Faloon



Serotonin is a compound in the brain that promotes feelings of personal security, relaxation, and confidence. A serotonin deficiency can result in sleep disturbance, anxiety, depression, and a propensity to overeat, particularly carbohydrates like simple sugars.

Startling research reveals that serotonin levels decline as we age!¹⁻³ These findings provide a biochemical rationale to explain common age-related disorders such as depressed mood and sleep difficulties. Based on these discoveries, aging people may appreciably improve their health by restoring serotonin to youthful levels.

The amino acid tryptophan is needed to produce serotonin in the brain.⁴ While the amount of tryptophan in a typical diet meets basic metabolic requirements, it often fails to provide optimal brain serotonin levels.

Ever since the FDA restricted the importation of tryptophan for use in dietary supplements, there has been an upsurge in the percentage of overweight and obese Americans.

One could argue that a widespread serotonin deficiency is at least partially responsible for the record numbers of depressed, sleep-deprived, and overweight individuals.

WHY DIETARY TRYPHTOPHAN IS INADEQUATE

Tryptophan is one of the eight essential amino acids found in the human diet. Essential amino acids are defined as those that cannot be made in the body and therefore must be obtained from food or supplements. (A ninth amino acid, histidine, is sometimes considered essential for children.)

Our bodies do need additional amino acids, but these other amino acids are made from the eight essential amino acids when we are in optimal health.

In any normal diet, be it omnivorous or vegetarian, tryptophan is the least plentiful of all amino acids. A typical diet provides only 1,000 to 1,500 mg/day of tryptophan, yet there is much competition in the body for this scarce tryptophan.

Tryptophan is used to make various protein structures of the body. In people with low-to-moderate intakes of vitamin B3(niacin), tryptophan may be used to make B3 in the liver at the astounding ratio of 60 mg tryptophan to make just 1 mg of vitamin B3.⁵

Yet even maintaining a minute amount of tryptophan provides little benefit in boosting serotonin in the brain due to competition with other amino acids for transport through the blood-brain barrier. Nutrients must be taken up through the blood-brain barrier by transport molecules. Tryptophan competes for these transport molecules with other amino acids.



THE HUMAN BODY REQUIRES THE FOLLOWING EIGHT ESSENTIAL AMINO ACIDS:

Tryptophan
Lysine
Methionine
Phenylalanine

Threonine
Valine
Isoleucine
Leucine

Essential amino acids cannot be made in the body and therefore must be obtained from food or supplements. (Children may require the amino acid histidine in addition to those listed above.)

As one can see, diet-derived tryptophan contributes very little actual tryptophan to the brain. As you will soon read, even eating tryptophan-containing foods like turkey may not always provide the body with enough of this essential amino acid. One reason is that aging people make enzymes that rapidly degrade tryptophan in the body.

Remember, tryptophan is the only normal dietary raw material for serotonin synthesis in the brain. Given all we now know about the difficulty in maintaining adequate tryptophan status, is it any wonder that so many aging humans suffer from disorders such as depression, insomnia, and excess weight gain associated with a serotonin deficiency?

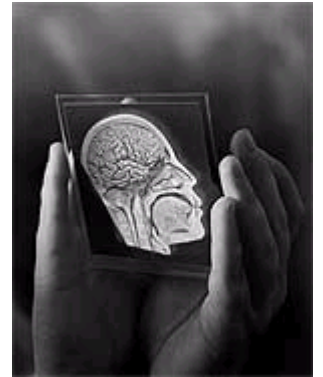
HOW TRYPTOPHAN FUNCTIONS IN THE BODY

L-tryptophan converts into serotonin, primarily in the brain. Since serotonin is a neurotransmitter involved in controlling moods and appetite, tryptophan supplementation has been recommended for individuals suffering from a variety of conditions associated with decreased serotonin levels, including sleep disorders, depression and fibromyalgia, and eating disorders.⁶⁻⁸

It has been shown in human clinical studies that low levels of tryptophan contribute to insomnia.⁹ Increasing tryptophan may help to normalize sleep patterns.¹⁰⁻¹² It is known that raising tryptophan levels in the body may decrease cravings and binge eating—especially for carbohydrates—and help people lose weight.^{13,14}

L-tryptophan serves as a precursor not only to serotonin, but also melatonin and niacin. Serotonin is a major neurotransmitter involved in many somatic and behavioral functions including mood, appetite and eating behavior, sleep, anxiety, and endocrine regulation.^{6,15-17}

There are two possible sources for L-tryptophan: diet and tissue proteins, from which L-tryptophan has been recycled during protein turnover. Aging, chronic inflammatory diseases, and HIV infection are associated with tryptophan depletion, even in the absence of dietary tryptophan deficiency.



An adult male needs 250 mg a day of tryptophan just to maintain nitrogen balance.¹⁸ While a normal diet contains 1,000 to 1,500 mg of tryptophan per day,¹⁹ the enzymatic breakdown of tryptophan increases with age,²⁰ and certain disease states can severely deplete tryptophan.

HOW TRYPTOPHAN IS METABOLIZED IN THE BODY

There are three potential fates for L-tryptophan once ingested:

- Incorporation into body tissue proteins.
- Conversion into serotonin (and melatonin).
- Conversion into indoleamines, carbon dioxide, water, adenosine triphosphate (ATP), and niacin.²¹

For every nutrient absorbed into the body, there are specific enzymes that convert the nutrient into other substances. There are two specific enzymes that can deprive the body of sufficient amounts of tryptophan. These enzymes are called L-tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO).

The liver enzyme TDO is induced when plasma concentrations of L-tryptophan exceed those needed for conversion into serotonin and/or protein. This enzyme oxidizes surplus L-tryptophan into carbon dioxide, water, and ATP.^{22,23}

The other tryptophan-degrading enzyme IDO is more insidious because it can degrade L-tryptophan even when circulating levels of L-tryptophan are low.^{23,24}

This enzyme has been found outside the liver on macrophages and dendritic cells and is increased in pro-inflammatory states, HIV infection, and normal aging.²⁵⁻³⁰

Once the TDO or IDO enzymes act on tryptophan, it is no longer available for conversion to serotonin or incorporation into protein. Consuming large amounts of oral L-tryptophan will not generate more serotonin because more TDO will be induced to

deplete the tryptophan.

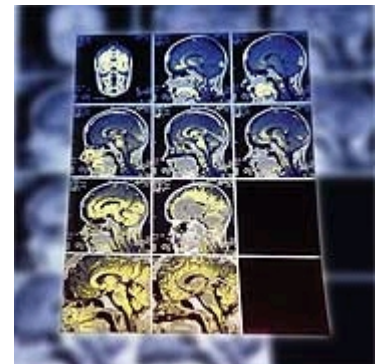
Tryptophan and its metabolite 5-hydroxytryptophan (5-HTP) are taken up into the brain across the blood-brain barrier by a transport system that is active towards all the large neutral amino acids.³¹ The affinity of the various amino acids for the carrier is such that there is competition between the large neutral amino acids for entry into brain. In fact, the best predictor of a given meal's effect on brain tryptophan-serotonin levels is the serum ratio of tryptophan to the pool of large neutral amino acids.³²

WHAT YOU NEED TO KNOW: TRYPTOPHAN

- Serotonin is a brain biochemical that promotes restful sleep, well-being, and satiety. When serotonin levels are low, people often experience depression, anxiety, insomnia, and the urge to overeat.
- The amino acid tryptophan is needed to produce serotonin in the body. While foods contain some tryptophan, the diet may not provide enough tryptophan to make adequate amounts of serotonin. Additionally, enzymes that are influenced by inflammation and aging can break down tryptophan before it converts to serotonin.
- Individuals suffering from the adverse effects of low serotonin levels can now restore sleep, appetite control, and mood by supplementing with an advanced L-tryptophan formulation. This formula combines L-tryptophan with nutrients and herbs that help optimize its ability to convert to beneficial serotonin in order to counteract appetite and sleep disorders, and low mood.

More clinically relevant, however, is that serotonin levels are enhanced by carbohydrate ingestion.³³ The reason is that the high amount of insulin released in response to carbohydrate ingestion accelerates the serum removal of valine, leucine, and isoleucine that compete against tryptophan for transport into the brain. Similarly, a higher percentage of protein in the diet slows serotonin elevation (by providing competing amino acids for the blood-brain barrier).^{34,35}

Giving tryptophan with an inhibitor of the TDO enzyme would enable lower doses of tryptophan to be used. In the rat, high doses of pyridoxine (vitamin B6) can inhibit tryptophan catabolism in the liver and increase uptake of tryptophan into the brain.³⁶ While the effect of high doses of pyridoxine on plasma tryptophan has not been studied in humans, pyridoxine should be given with tryptophan for another reason. When tryptophan was given to normal subjects for a week, levels of tryptophan metabolites in the plasma increased indicating that tryptophan was being broken down. This effect could be attenuated by pyridoxine (pyridoxine assists the breakdown of the tryptophan metabolite kynurenine, which can compete with tryptophan for uptake into the brain), suggesting that chronic tryptophan treatment increases pyridoxine requirements.³⁷



CLINICAL IMPLICATIONS: SLEEP DISORDERS

Tryptophan has been researched for sleep disorders for 30 years. Improvement of sleep normalcy has been noted³⁸ at doses as low as 1,000 mg.¹⁹ Increased stage 4 sleep has been noted at even lower doses—as low as 250 mg tryptophan.¹⁹ Significant improvement in obstructive sleep apnea, but not central sleep apnea, has been noted at doses of 2,500 mg at bedtime, with those experiencing the most severe apnea demonstrating the best response.³⁹ While many sedative medications have opioid-like effects, L-tryptophan administration does not limit cognitive performance or inhibit arousal from sleep.⁴⁰

L-tryptophan depletion negatively impacts sleep. A significant decrease in serum tryptophan levels after a tryptophan-free amino acid drink was associated with an adverse effect upon sleep parameters (stage 1 and stage 2 time, and rapid eye movement sleep time).⁹ L-tryptophan is not associated with tolerance or difficulty with morning waking and has been shown to be efficacious for sleep in several clinical trials of various designs and L-tryptophan dosages.

DEPRESSION

As previously mentioned, L-tryptophan is essential for the brain to synthesize serotonin, a neurotransmitter that has been shown to affect mood. Several studies have shown that acute tryptophan depletion can cause a depressive state in humans, especially patients who are in remission from depression.^{41,42} In a study of the effects of acute tryptophan depletion on healthy women and patients with bulimia nervosa, both groups were given amino acid mixtures to consume to decrease their plasma tryptophan levels. In both groups an increase in depression occurred.⁴³

Plasma L-tryptophan levels can be raised through dietary intake of L-tryptophan, which raises serotonin levels in the brain, and thereby lessens the depressive state.⁴⁴ In a study involving recovering alcoholic patients, it was found that the participants had severely depleted L-tryptophan levels accompanied by a high level of depressive state. When the patients were given supplemental doses of L-tryptophan over a short period of time, their depressive state lessened significantly.⁴⁵ The tryptophan metabolite, 5-hydroxytryptophan (5-HTP), has shown significant clinical response for depression in 2-4 weeks, at doses of 50-300 mg three times daily.⁴⁶⁻⁴⁸



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PREMENSTRUAL SYNDROME

A daily dose of 6,000 mg of L-tryptophan significantly decreased mood swings, tension, and irritability in women with premenstrual syndrome.⁴⁹ The metabolism of tryptophan is impacted by the different phases of a woman's cycle,⁵⁰ and therefore hormonal changes during the menstrual cycle may negatively affect the availability of tryptophan for conversion into serotonin.

CARBOHYDRATE CRAVINGS AND WEIGHT LOSS

Some obese people consume carbohydrate-rich foods frequently and preferentially, because they have a persistently low plasma tryptophan ratio, as well as low tryptophan uptake into the brain.⁵¹ Remember that serotonin levels are enhanced by carbohydrate ingestion as insulin release accelerates the serum removal of other amino acids that compete for transport through the blood-brain barrier.

Increasing the L-tryptophan levels in blood plasma is also known to have an appetite-suppressing effect that mainly impacts carbohydrate consumption.^{52,53} Presumably the supplemental tryptophan would enhance the release of serotonin from brain neurons to diminish appetite for carbohydrates, which helps with loss of body weight. In addition, obese subjects are often insulin-resistant, and diminished insulin action may cause low plasma tryptophan ratios³³ because of the peripheral effects of insulin on the uptake and utilization of other amino acids.

A study was done to measure L-tryptophan in the blood plasma of obese patients to assess the plasma tryptophan ratio to large neutral amino acids (tyrosine + phenylalanine + leucine + isoleucine + valine). The results showed the plasma tryptophan ratio was well below the normal ratio for humans.⁵¹ If elevation of the tryptophan in relation to large neutral amino acids occurs, more tryptophan is allowed into the brain to induce serotonin synthesis and influence functions of serotonin (mood, appetite, sleep, and hunger). This study helps show why obese people often have uncontrollable appetites, i.e., they have too little tryptophan in relation to other large neutral amino acids in their blood.

When these obese patients were given 1,000 mg, 2,000 mg, or 3,000 mg doses of L-tryptophan one hour before meals to raise the amount of tryptophan relative to the large neutral amino acids, a significant decrease in caloric consumption was observed. The majority of the reduction in caloric intake was due to the amount of carbohydrates, not protein, consumed. The only side effects observed were a mild decrease in mental alertness, mild dizziness, and mild drowsiness.⁵⁴

In a double-blind, placebo-controlled study, obese patients on protein-rich diets who received tryptophan (750 mg twice daily orally) had significant weight loss, compared with a placebo group. A moderate dose of tryptophan supplementation did not cause any side effects such as mid-day sleepiness or fatigue.⁵⁵ The effects of reducing tryptophan levels were also studied in a 7-year-old girl with severe anorexia. When tryptophan levels were reduced, spontaneous eating occurred for the first time in 4.5 years. The spontaneous eating ceased when the tryptophan intake was increased.⁵⁶

HOW AGING REDUCES TRYPTOPHAN-SEROTONIN LEVELS

As a result of normal aging, inflammatory cytokine levels increase. A little-known adverse effect is that inflammatory cytokines (such as tumor necrosis factor alpha and interferon alpha) cause induction of the tryptophan-degrading enzyme IDO (indoleamine 2,3-dioxygenase).

You might think that aging people could compensate for the tryptophan-degrading effects of IDO by consuming higher doses of tryptophan supplements. The problem is that in the presence of high blood levels of tryptophan, the other tryptophan-degrading enzyme TDO is also elevated.

So consuming large amounts of L-tryptophan (oral doses of 4,000 mg and greater) will not generate more serotonin because TDO will be induced. Yet if aging people fail to get more tryptophan into their bodies, brain serotonin levels will plummet because the higher IDO enzyme activity will degrade what little tryptophan remains in the blood.

ENGINEERING AROUND THIS PROBLEM

Fortunately, the new understanding of how tryptophan is degraded in aging humans provides a basis for engineering a natural solution around this epidemic problem.

First of all, we know from studies in patients with high levels of systemic inflammation that if sufficient niacinamide is given, the degradation of tryptophan in the body is significantly reduced.^{57,58} We also know that the amino acid lysine competes with tryptophan in the same oxidative degradation pathway. This means that in the presence of lysine, less tryptophan is oxidized.⁵⁹

Tryptophan, however, can still be degraded by the IDO enzyme that increases as humans age. Nutrients such as curcumin inhibit interferon-induced nuclear factor-kappa-B and COX-2 expression and may limit the induction of IDO, thus making more tryptophan available for conversion to serotonin in the brain.⁶⁰

It is thus possible for aging people to supplement with a modest dose of tryptophan (1,000-1,500 mg per day) and significantly decrease tryptophan oxidation/degradation, as long as lysine, niacinamide, and the proper cytokine-suppressing nutrients are taken with it to neutralize the effects of the IDO enzyme.

Cofactors that facilitate the conversion of tryptophan to serotonin in the brain are vitamin B6, magnesium, and vitamin C.⁶⁰⁻⁶² These nutrients are already taken by most health-conscious people.

DOSAGE

An important factor in the decision to supplement with L-tryptophan is its excellent tolerability and the lack of development of tolerance during long-term use. Furthermore, L-tryptophan does not cause difficulties when trying to wake up the next morning.⁶³

The minimal dose of L-tryptophan for effective treatment of insomnia may be at least 1,000 mg, and repeat administration of L-tryptophan may be required for improvement in chronic, well-established, sleep-onset insomnia or insomnia characterized by both sleep-onset and sleep-maintenance abnormalities.⁶³ Low doses of L-tryptophan (250 to 500 mg) may not offer a significant benefit on sleep latency.⁶⁴ For those with insomnia who wish to try L-tryptophan, a strong initial dose (1,000 to 4,000 mg) is recommended for the first week, followed by a lower maintenance dose (500 mg to 1,000 mg).

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 1,000-3,000 mg daily. Safe and effective dosages for other disorders range from 500 mg to 4,000 mg/day, while doses around 3,500 mg/day have been used short term as a smoking cessation intervention.⁶⁵

Tryptophan is oxidized in the liver by tryptophan-2,3-dioxygenase (TDO), an enzyme that is induced both by glucocorticoids and by large doses of tryptophan itself. The enzyme activity of TDO increases after tryptophan administration⁶⁶ and results in a relatively short half-life of tryptophan remaining in the plasma.⁶⁷ Thus, tryptophan is often given in divided daily doses instead of a single dose. A single dose of 3,000 mg is sufficient to keep human brain serotonin synthesis maximized for about eight to twelve hours.⁶⁸ Giving three daily doses of 2,000 mg will probably keep the rate-limiting tryptophan hydroxylase enzyme in the brain fully saturated for most of each 24-hour period, meaning that brain serotonin levels would be maintained at a constant optimal level.

TRYPTOPHAN BLACKOUT IS LIFTED!

American consumers can once again obtain tryptophan as a dietary supplement. Particularly compelling news is the discovery that aging people produce tryptophan-degrading enzymes, which can be neutralized by the simultaneous ingestion of nutrients that block pro-inflammatory cytokines and mitigate tryptophan depletion via other oxidative pathways.

A novel formula is now available that combines pharmaceutical-pure tryptophan with a blend of nutrients designed to nourish the brain with optimal levels of serotonin.

Based on hundreds of scientific studies, depletion of serotonin may contribute to age-related weight gain, depression, insomnia, anxiety, and loss of feeling of well-being.

By restoring serotonin to optimal levels, aging people can regain the neurotransmitter balance enjoyed in their youth. Those suffering from age-related weight gain or sleep difficulties could experience significant improvement by using tryptophan to increase their brain serotonin to youthful levels.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

To learn who should not take high-dose tryptophan supplements, refer to the Tryptophan Precautions section on the following page.

TRYPTOPHAN PRECAUTIONS

For many decades, tens of millions of people have safely used tryptophan supplements. The mechanisms by which tryptophan functions in the body, however, indicate that those taking certain prescription drugs should exercise caution when using tryptophan on a regular basis.

Although tryptophan has been shown to be safe when used alone, it can potentiate side effects of certain antidepressant drugs. Case reports of serotonin syndrome have noted a connection between tryptophan used concomitantly with monoamine oxidase (MAO) inhibitor drugs.⁶⁹ A few popularly prescribed MAO-inhibiting drugs include Nardil® (phenelzine), Parnate® (tranylcypromine), and Marplan® (isocarboxazide). In studies measuring the antidepressant effects of an MAO-inhibitor drug alone compared with that of the MAO inhibitor plus tryptophan, the most common side effects of the combination were dizziness, nausea, and headache.⁷⁰ The magnitude of these side effects was sufficient to limit the usefulness of the combination. However, the most serious complication in the use of the combination of tryptophan and MAO inhibitors is the serotonin syndrome. This syndrome is characterized by agitation, restlessness, shivering and tremor, confusion, delirium, tachycardia, diaphoresis, hypomania, myoclonus, hyperreflexia, 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) drug such as Prozac®, Paxil®, Zoloft®, or Lexapro®, may also precipitate serotonin syndrome.⁷¹

The serotonin syndrome was first described in rats. When these animals were given tryptophan plus a monoamine oxidase inhibitor, or various other drugs including high doses of 5-hydroxytryptophan (5-HTP) (with a peripheral decarboxylase inhibitor drug), or serotonin-receptor agonists, the animals exhibited tremor, rigidity, hypertonicity, hind-limb abduction, rigidly arched tail, lateral head shaking, treading movements of the forelimbs, hyperreactivity, myoclonus, and even generalized seizures.⁷²

The appearance of the serotonin syndrome in 38 patients in 12 reports has been reviewed.⁷³ The majority of these cases were associated with patients taking a combination of tryptophan and an MAO-inhibitor drug, but the combination of serotonin-reuptake inhibitor and MAO-inhibitor drugs can also cause the serotonin syndrome. The incidence of the serotonin syndrome in patients is unknown, but some experts argue that it is under-reported, perhaps because it is not recognized, or possibly because it is confused with the neuroleptic malignant syndrome, which has some similarities in terms of symptoms.

The serotonin syndrome usually resolves within 24 hours of cessation of tryptophan treatment, with no residual symptoms. Although the animal model suggests that serotonin antagonists should be a useful treatment, this has not been tested in humans. Supportive measures have been used including cooling for hypothermia, intramuscular chlorpromazine as an antipyretic and sedative, artificial ventilation for respiratory insufficiency, anticonvulsants for seizures, clonazepam for myoclonus, and nifedipine for hypertension.⁷³

Although the serotonin syndrome has been reported in patients taking tryptophan and an MAO-inhibitor drug, the incidence of this disorder is low. The total number of patients in the literature reporting symptoms of the serotonin syndrome after taking tryptophan and an MAO-inhibitor drug is less than 40. This is in spite of the fact that tryptophan has been on the market as an antidepressant in the United Kingdom for over 20 years, and psychiatrists in that country are more likely than psychiatrists in North America to use MAO-inhibitor drugs.

Moreover, in the clinical trials on the combination of tryptophan and an MAO-inhibitor drug, there is only one report of symptoms resembling the serotonin syndrome in spite of the very large doses of tryptophan used (up to 18,000 mg of tryptophan per day).⁷⁴ There have been no reports of permanent effects after the serotonin syndrome was resolved in patients receiving tryptophan and an MAO-inhibitor drug, although deaths have been seen after the serotonin syndrome in patients who were given MAO-inhibitor and tricyclic antidepressant drugs.

INTERACTION WITH HERBS

Tryptophan may cause excessive sedation if it is taken with potentially sedating herbs such as catnip, kava kava, St. John's wort, or valerian.⁷⁵

WARNINGS AND CONTRAINDICATIONS

Patients with liver cirrhosis should avoid tryptophan supplementation. Cirrhotic liver disease patients present with reduced activity of tryptophan 2,3-dioxygenase (22%), with subsequent increased free tryptophan and half-life, and decreased clearance.⁷⁶ Tryptophan is known to pass into the breast milk of new mothers, but its possible effects in infants are not known. Therefore, tryptophan should also be avoided during breast-feeding. Tryptophan may cause sedation, which may result in sleepiness or mental confusion during the daytime. Individuals who choose to take it should be careful when driving or

performing other tasks that require alertness.

TOXICOLOGICAL STUDIES

L-tryptophan has low oral toxicity. A rat carcinogenicity bioassay conducted by the US National Cancer Institute found no evidence of cancer causation.⁷⁷

SIDE EFFECTS

Potential side effects of L-tryptophan at high doses (100 mg/kg/day or 7,000 mg taken by a 150-pound person) include gastric irritation, vomiting, and head twitching.⁷⁸ Less severe side effects include:

- Blurry vision
- Daytime drowsiness
- Dry mouth
- Headaches
- Muscle incoordination
- Nausea

EOSINOPHILIA MYALGIA SYNDROME

In early 1990s, taking tryptophan was considered to be associated with a severe condition known as eosinophilia myalgia syndrome (EMS).⁶⁵ Although the exact causes for the outbreak are still not completely known, it is believed that a defective manufacturing process used by one company either introduced contaminants or caused reactions that formed toxic substances within the tryptophan that was produced. However, an independent scientific committee on toxicity recently concluded that tryptophan has not resulted in a detectable increase in risk of EMS, and that pure tryptophan preparations are safe.

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