

5-hydroxytryptophan / Serotonin

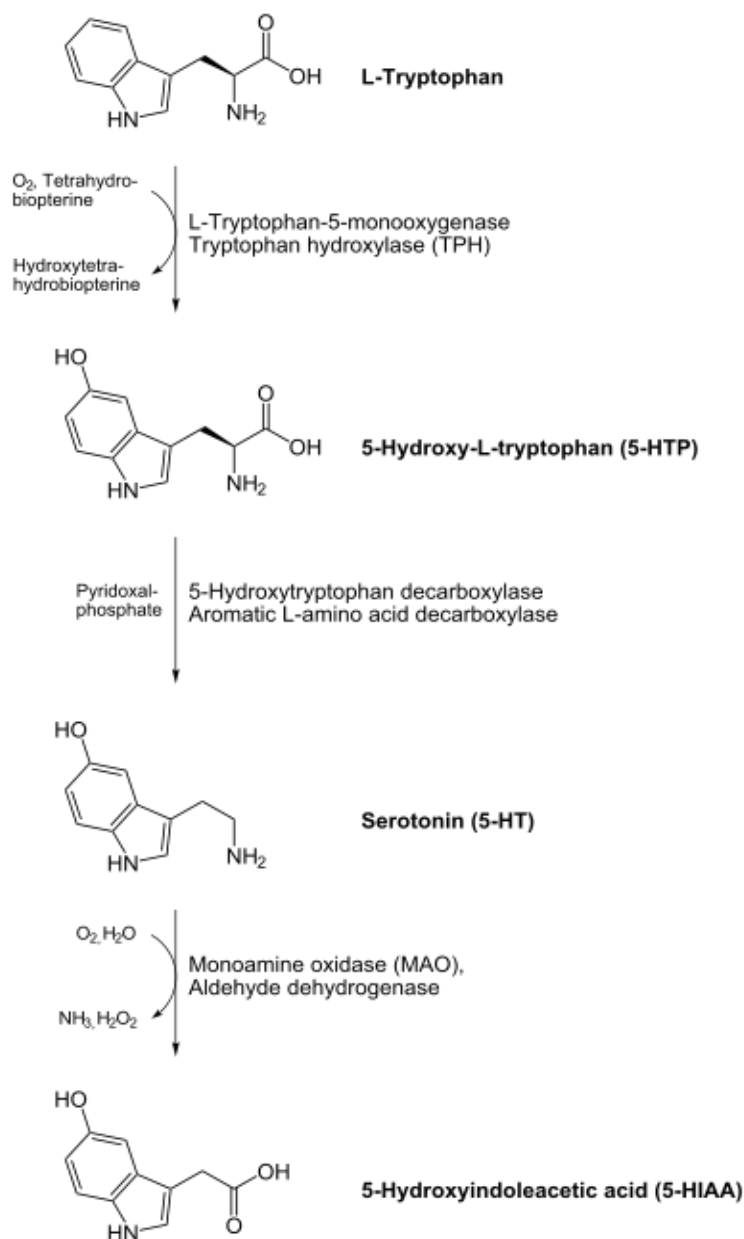
Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter. 5-HT is released from platelets exposed to thrombin in the coagulation process. It is found in the argentaffin cells of the GIT. Increased concentration of 5-HT is present in the wall of the intestine (in the enterocromaffin cells), blood and CNS. Also present in mast cells of rats, mice and bovines where 5-HT is released during anaphylaxis. *Caenorhabditis elegans* worms artificially depleted of serotonin behave like animals living in a low-food environment. They move around more, and mating and egg-laying is suppressed. The opposite happens if serotonin is increased in animals.

In humans serotonergic signaling plays an important role in the modulation of mood, anger and aggression. Serotonin also has effects on appetite, sleep and metabolism. The action of serotonin on the worms mating and egg-laying is similar to that of human sexuality. Drugs targeting serotonin-induced pathways are being used in the treatment of many psychiatric disorders, and one focus of clinical research is the influence of genetics on serotonin action and metabolism in psychiatric settings. Levels of serotonin in the brain show association with aggression, and a mutation in the gene which codes for the 5-HT_{2A} receptor may double the risk of suicide for those with that genotype.

In case of bleeding they release it, which makes the blood vessel to constrict. If something in the food irritates the enterochromaffin cells they release large amounts of serotonin to increase peristaltic movements so that the gut empties. If intestinal serotonin leaks out to the bloodstream faster than the platelets can absorb it large amounts of free serotonin will be present in the blood. This activates 5HT₃ receptors in the chemoreceptor trigger zone which stimulates vomiting. As can be expected from a substance indicating nutrient availability, serotonin also acts as a growth factor. If the liver is damaged its cells start to express 5-HT_{2A} and 5-HT_{2B} receptors.

Biosynthesis

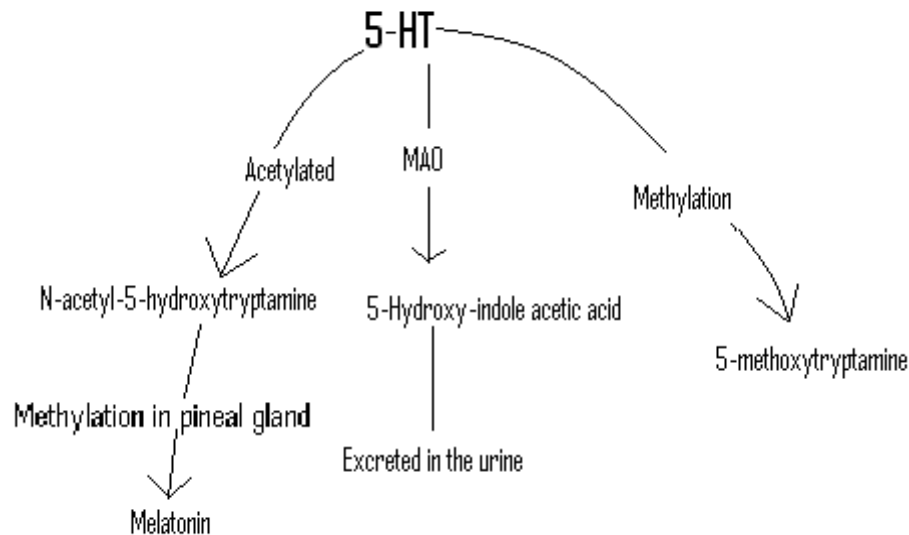
Serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and L-aromatic amino acid decarboxylase. The TPH-mediated reaction is the rate-limiting step in the pathway. TPH exists in two forms: TPH1, found in several tissues, and TPH2, which is a brain-specific isoform. Genetic polymorphisms in both these subtypes influence susceptibility to anxiety and depression in humans. Ovarian hormones can affect the expression of TPH in various species, suggesting a possible mechanism for postpartum depression and pre-menopausal syndrome.



Serotonin taken orally does not pass into the serotonergic pathways of the central nervous system because it does not cross the blood-brain barrier. However, tryptophan and its metabolite 5-hydroxytryptophan (5-HTP), from which serotonin is synthesized, can cross the blood-brain barrier. These agents are available as dietary supplements and may be effective serotonergic agents.

One product of serotonin breakdown is 5-Hydroxyindoleacetic acid (5 HIAA), which is excreted in the urine. Serotonin and 5 HIAA are sometimes produced in excess amounts by certain tumors or cancers, and levels of these substances may be measured in the urine to test for these tumors.

Metabolism:



Receptors

With the exception of the 5-HT₃ receptor, a ligand gated ion channel, all other 5-HT receptors are G protein coupled seven trans membrane receptors that activate an intracellular second messenger cascade.

Drugs targeting the 5-HT system

Psychedelic drugs

Psilocin/Psilocybin, DMT, mescaline, and LSD - agonists at 5-HT_{2A}-receptor.

Antidepressants

The MAOIs prevent the breakdown of monoamine neurotransmitters (including serotonin), and therefore increase concentrations of the neurotransmitter in the brain. MAOI therapy causes many adverse drug reactions, and patients are at risk of hypertensive emergency triggered by foods with high tyramine content and certain drugs.

The tricyclic antidepressants (TCAs) inhibit the re-uptake of both serotonin and norepinephrine. The newer selective serotonin re-uptake inhibitors (SSRIs) have fewer side-effects and fewer interactions with other drugs.

Selective serotonin reuptake *enhancer*, Tianeptine, is a novel antidepressant having mood elevating effects.

Antiemetics

Ondansetron, granisetron, and tropisetron are important antiemetic agents active as 5-HT₃ antagonists. They are used to treat nausea and vomiting during anticancer chemotherapy using cytotoxic drugs. Also used in the treatment of post-operative nausea and vomiting.

Chronic diseases resulting from serotonin 5-HT_{2B} overstimulation

Cardiac fibrosis

Serotonin may cause a syndrome of cardiac fibrosis when it is eaten in large quantities in the diet (the Matoki banana of East Africa) or when it is over-secreted by certain mid-gut carcinoid tumors. The valvular fibrosis is on the right side of the heart, since excess serotonin in the serum outside platelets is metabolized in the lungs, and does not reach the left circulation.

The serotonergic vasoconstrictive anti-migraine drugs (ergotamine and methysergide), the serotonergic appetite suppressant drugs (fenfluramine, chlorphentermine, and aminorex), and certain anti-parkinsonian dopaminergic agonists (pergolide and cabergoline), which stimulate serotonergic 5-HT_{2B} receptors have been linked with these syndromes.

