

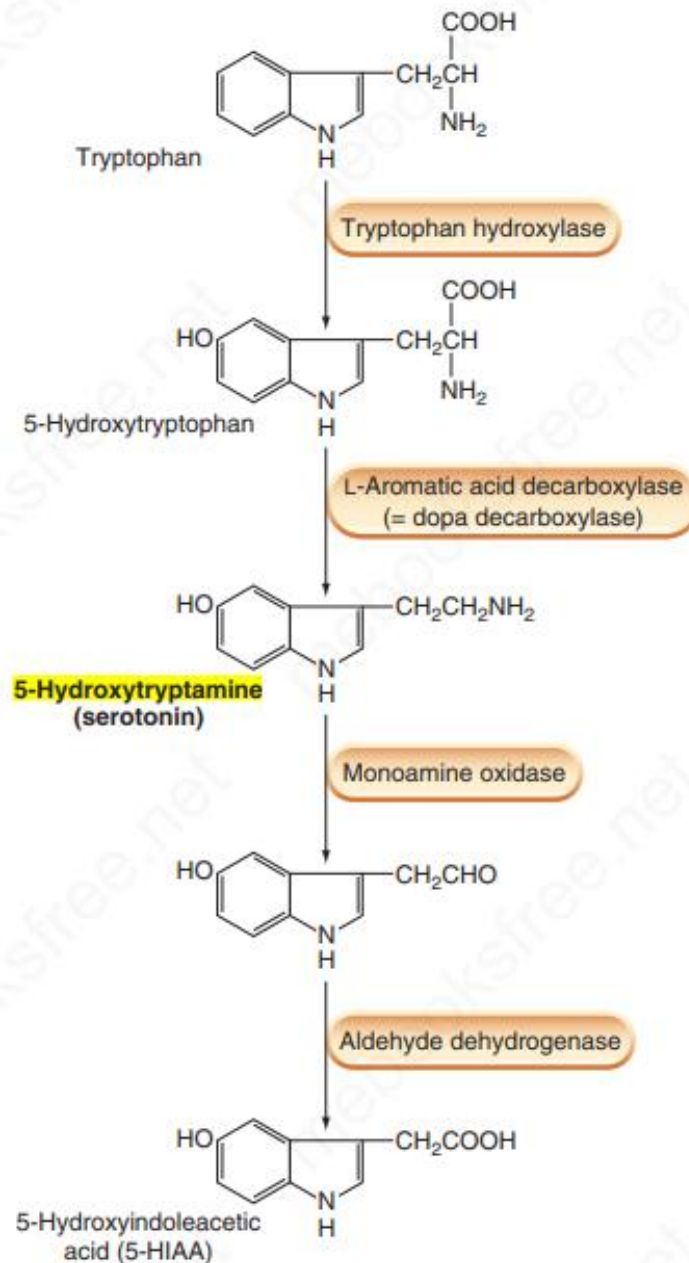
5-HYDROXYTRYPTAMINE

A biogenic amine, originally detected in blood serum ('serotonin') and extracts of gut ('enteramine') was eventually identified chemically as 5-hydroxytryptamine. The terms '5-HT' and 'serotonin' are used interchangeably. It also acts as a local hormone ('autocoid') and is important in platelet function.

Chemistry & Pharmacokinetics (BIOSYNTHESIS, METABOLISM and DISTRIBUTION)

Biosynthesis: Tryptophan is converted to 5-hydroxytryptophan in chromaffin cells and neurons by the action of tryptophan hydroxylase, an enzyme confined to 5-HT-producing cells (but not present in platelets). The 5-hydroxytryptophan is then decarboxylated to 5-HT by the dopa decarboxylase.

Metabolism of 5-HT, occurs mainly by the **MAO-A**, followed by oxidation to 5-hydroxy-indole-acetic acid (5-HIAA). 5-HIAA is excreted in the urine, which serves as an indicator of 5-HT production in the body. This is used, for example, in the diagnosis of carcinoid tumor of enterochromaffin cells (treatment includes use of 5-HT antagonist)



Platelets (and neurons) possess a high-affinity 5-HT uptake mechanism. They become loaded with 5-HT as they pass through the intestinal circulation.

However, selective serotonin reuptake inhibitors (SSRIs) have been developed and are important therapeutically as anxiolytics and antidepressants.

5-HT is often stored in neurons and chromaffin cells as a co-transmitter, together with various peptide hormones, such as somatostatin, substance P or vasoactive intestinal polypeptide

The highest concentrations of 5-HT are **found mainly in three organs:**

- **In the wall of the intestine.** Over 90% of the total amount in the body is present in the enterochromaffin cells
- **In blood.** Platelets contain high concentrations of 5-HT, hence the high concentration of 5-HT in serum from clotted blood.
- **In the CNS.** 5-HT is a transmitter in the CNS and is present in high concentrations in localised regions of the midbrain and play versatile role like in Mood, sleep, appetite, temperature regulation.

Actions and functions of 5-hydroxytryptamine (5-HT)

• Important actions are:

- increased gastrointestinal motility
- contraction of other smooth muscle (like bronchi, uterus)
- mixture of vascular constriction and dilatation (endothelium dependent)
- platelet aggregation
- stimulation of peripheral nociceptive nerve endings
- excitation/inhibition of central nervous system neurons.

• Postulated physiological and pathophysiological roles include:

- in periphery: peristalsis, vomiting, platelet aggregation and haemostasis, inflammation, sensitisation of nociceptors and microvascular control
- in central nervous system: many postulated functions, including control of appetite, sleep, mood, hallucinations, stereotyped behaviour, pain perception and vomiting.

• Clinical conditions associated with disturbed 5-hydroxytryptamine (5-HT) include:

- migraine, carcinoid syndrome, pulmonary hypertension, mood disorders and anxiety

5-HT RECEPTORS

These are divided into seven classes (5-HT₁–7), one of which (5-HT₃) is a ligand-gated cation channel while the remainder are G protein-coupled receptors (GPCRs). The six GPCR families are further subdivided into some 13 receptor subtypes based on their sequence and pharmacology.

Most 5-HT GPCRs signal through adenylyl cyclase/cAMP, but some (the 5-HT₂ subtype) activate phospholipase C to generate phospholipid-derived second messengers

Receptor	Location	Main function	Primary signalling system	Significant drugs	
				Agonists	Antagonists
5-HT _{1A}	Chiefly CNS	Neuronal inhibition Behavioural effects: sleep, feeding, thermoregulation, anxiety	G protein (G _i /G _o) ↓ cAMP (may also modulate Ca ²⁺ channels)	8-OH-DPAT, triptans, clozapine, buspirone (PA), cabergoline	Methiothepin, yohimbine, ketanserin, pizotifen, spiperone
5-HT _{1B}	CNS, vascular smooth muscle, many other sites	Presynaptic inhibition Behavioural effects Pulmonary vasoconstriction	G protein (G _i /G _o) ↓ cAMP (may also modulate Ca ²⁺ channels)	8-OH-DPAT, triptans (PA), clozapine, cabergoline, dihydroergotamine	Methiothepin (IA), yohimbine, ketanserin, spiperone
5-HT _{1D}	CNS, blood vessels	Cerebral vasoconstriction Behavioural effects: locomotion	G protein (G _i /G _o) ↓ cAMP (may also modulate Ca ²⁺ channels)	8-OH-DPAT, triptans, clozapine, cabergoline (PA), dihydroergotamine/ ergotamine	Methiothepin (IA), yohimbine, ketanserin, methysergide, spiperone
5-HT _{1E}	CNS	—	G protein (G _i /G _o) ↓ cAMP (may also modulate Ca ²⁺ channels)	8-OH-DPAT, triptans; clozapine, dihydroergotamine	Methiothepin, yohimbine, methysergide
5-HT _{1F}	CNS, uterus, heart, GI tract	—	G protein (G _i /G _o) ↓ cAMP (may also modulate Ca ²⁺ channels)	8-OH-DPAT, triptans; clozapine dihydroergotamine/ ergotamine, lamistidan	Yohimbine, methysergide
5-HT _{2A}	CNS, PNS, smooth muscle, platelets	Neuronal excitation Behavioural effects Smooth muscle contraction (gut, bronchi, etc.) Platelet aggregation Vasoconstriction/vasodilatation	G protein (G _q /G ₁₁) ↑ IP ₃ , Ca ²⁺	LSD, cabergoline, methysergide (PA), 8-OH-DPAT, ergotamine (PA)	Ketanserin, clozapine, methysergide
5-HT _{2B}	Gastric fundus	Contraction	G protein (G _q /G ₁₁) ↑ IP ₃ , Ca ²⁺	LSD, cabergoline, methysergide (PA), 8-OH-DPAT, ergotamine (PA)	Ketanserin, clozapine, yohimbine
5-HT _{2C}	CNS, lymphocytes	—	G protein (G _q /G ₁₁) ↑ IP ₃ , Ca ²⁺	LSD, cabergoline, methysergide (PA), 8-OH-DPAT, ergotamine (PA)	Ketanserin, clozapine (IA), methysergide
5-HT ₃ (recently renamed 5-HT _{3A})	PNS, CNS	Neuronal excitation (autonomic, nociceptive neurons) Emesis Behavioural effects: anxiety	Ligand-gated cation channel	2-Me-5-HT, chloromethyl biguanide	Granisetron, ondansetron, palonosetron.
5-HT ₄	PNS (GI tract), CNS	Neuronal excitation GI motility	G protein (G _s) ↑ cAMP	Metoclopramide, tegaserod (PA), cisapride	Tropisetron
5-HT _{5A}	CNS	Modulation of exploratory behaviour (rodents)?	G protein (G _s) ↑ cAMP	Triptans, 8-OH-DPAT	Clozapine, methysergide, yohimbine, ketanserin
5-HT ₆	CNS, leukocytes	Learning and memory, modulation of neurotransmission.	G protein (G _s) ↑ cAMP	LSD, ergotamine	Clozapine (IA), spiperone, methysergide, dihydroergotamine
5-HT ₇	CNS, GI tract, blood vessels	Thermoregulation? Circadian rhythm?	G protein (G _s) ↑ cAMP	Buspirone (PA), bromocriptine, cisapride, 8-OH-DPAT, LSD,	Clozapine (IA), methysergide, buspirone, dihydroergotamine, ketanserin, yohimbine

Source: Rang and Dale Pharmacology