

Serotonin Synthesis and Metabolism

Key References

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Overview

Serotonin (5-hydroxytryptamine) is principally found stored in three main cell types - (a) serotonergic neurons in the CNS and in the intestinal myenteric plexus, (b) enterochromaffin cells in the mucosa of the gastrointestinal tract and (c) in blood platelets. Serotonergic neurons and enterochromaffin cells can synthesize serotonin from its precursor amino acid L-tryptophan, whereas platelets rely upon uptake of serotonin for their stores. Likewise, serotonergic neurons also have the capacity for amine uptake via serotonin transporters. Serotonin is also synthesized in the pineal gland as a precursor for the subsequent enzymatic formation of the pineal hormone melatonin (N-acetyl-5-methoxytryptamine).

The biochemical pathway for serotonin synthesis initially involves the conversion of L-tryptophan to 5-hydroxytryptophan by the enzyme L-tryptophan hydroxylase. This enzyme provides the rate limiting step for serotonin synthesis, in the same manner that norepinephrine and dopamine synthesis in adrenergic and dopaminergic neurons is controlled by the ability of the related enzyme, L-tyrosine hydroxylase, to convert L-tyrosine to L-dihydroxyphenylalanine (L-DOPA). Some inhibitors of tryptophan hydroxylase (e.g. α -propyl-dopacetamide) are also active against tyrosine hydroxylase, whereas others such as *p*-chlorophenylalanine are more selective for tryptophan hydroxylase. Although *p*-chloroamphetamine and fenfluramine can also inhibit tryptophan hydroxylase, they have important actions (including neurotoxic effects) upon various other regulatory processes of serotonergic neuronal function. The subsequent metabolic step in the synthesis of serotonin (and also norepinephrine or dopamine)

involves the decarboxylation of 5-hydroxytryptophan (and L-DOPA) by the action of the enzyme L-aromatic amino acid decarboxylase. Inhibitors of this enzyme include the drugs benserazide and carbidopa, which do not cross the blood brain barrier, and are used clinically to prevent peripheral decarboxylation of the L-DOPA administered as a precursor for central dopamine formation in Parkinsonian patients.

Metabolism of serotonin is carried out primarily by the enzyme monoamine oxidase (MAO), which occurs as two molecular subtypes called MAO-A and MAO-B, which have some differences in their tissue and cellular distributions. MAO-A is more selective for serotonin oxidation by being able to metabolize serotonin with a much lower K_m value (and higher affinity for the substrate) than MAO-B. Inhibition of MAO-A activity to prevent serotonin metabolism in the CNS is believed to be linked to the antidepressant properties of a number of subtype selective (e.g. moclobemide) and nonselective (e.g. phenelzine) MAO inhibitors in clinical use. Interestingly, however, immunohistochemical studies have suggested that serotonin-containing neurons may themselves contain only MAO-B. The action of MAO converts serotonin to 5-hydroxyindole acetaldehyde which in turn is readily metabolized by aldehyde dehydrogenase to produce 5-hydroxyindole acetic acid as the major excreted metabolite of serotonin. An alternative metabolic route via aldehyde reductase can convert 5-hydroxyindole acetaldehyde to 5-hydroxytryptophol, but this pathway is normally considered to be insignificant.

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COMPOUND	ENZYME	CO-FACTORS	INHIBITORS
L-Tryptophan (T 0254)	Tryptophan-5-hydroxylase	Oxygen Tetrahydrobiopterin (T 4425)	<i>p</i> -Chlorophenylalanine (C 8655) <i>p</i> -Ethinylphenylalanine α -Propylidopacetamide (D 0385) 6-Fluorotryptophan (F 7626) <i>p</i> -Chloroamphetamine (C 9635) Fenfluramine (F 8507)
5-Hydroxytryptophan (H 9772)	L-Aromatic amino acid decarboxylase	Pyridoxal phosphate (P 9255)	Benserazide (Ro 4-4602) (B 7283) Brocresine Carbidopa (C 1335) Difluoromethylidopa 3-Hydroxybenzylhydrazine (NSD 1015) (H 9382) α -Methylidopa (M-129) Monofluoromethylidopa
5-Hydroxytryptamine (H 9523)	Monoamine oxidase A	Oxygen FAD (F 6625)	MAO-A SELECTIVE Clorgyline (M 3778) Harmaline (H 1392) Moclobemide Brofaromine Toloxatone Befloxatone Ro 41-1049 (R-107) MAO-A/B Non-SELECTIVE Iproniazid (I 7627) Phenelzine (P 6777) Isocarboxazid Nialamide (N 1392) Tranylcypromine (P 8511) 6-Methoxy-tetrahydro-9H pyrido-indole _(29,155-2)
5-Hydroxyindoleacetaldehyde	Aldehyde dehydrogenase (A 9770)	NAD+ (N 7004)	Disulfiram (T 1132) Cyanamide (C 1920) Daidzin (D 7802) Genistin (G 0897) Propionaldehyde (30,360-7) Phenethyl isothiocyanate (25,373-1) Methylene blue (MB-1)
5-Hydroxyindoleacetic acid (H 8876)			

Abbreviation:

Ro 41-1049: N-(2-Aminoethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide