

# Histamine Synthesis and Metabolism

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## Overview

Histamine is a biogenic amine that stimulates multiple histamine receptor types. In mammals, histamine is found within granules of basophils and mast cells (>90% of body stores) and within tuberomammillary neurons of the CNS. When released, histamine induces complex physiological and pathological effects, including allergic reactions, gastric acid secretion, multiple CNS-regulated effects, smooth muscle contraction and profound vasodilation that can lead to cardiovascular collapse.

In mammals, physiological levels of L-histidine are converted to histamine by specific L-histidine decarboxylase (HD; E.C. 4.1.1.22), which differs from the nonspecific DOPA decarboxylase (E.C. 4.1.1.26).  $\alpha$ -Fluoromethylhistidine ( $\alpha$ -FMH) has been shown to be an irreversible, highly selective 'suicide' inhibitor of HD, although this mode of inhibition often has little or no immediate effect on histamine stores or transmission. Once released, histamine is metabolized almost exclusively by methylation or oxidation, the propensity of which varies between species and between tissues and organs within species. For example, in brain relatively small amounts of histamine are oxidized with most being methylated. As a survival mechanism, only traces of histamine escape metabolism, particularly following systemic injection or release, with inhibition of one metabolic route resulting in histamine being shunted to another.

Histamine is methylated at the imidazole nitrogen furthest from the ethylamine side chain (termed tele-N or N<sup>+</sup>) by the enzyme histamine-N-methyltransferase (HMT; E.C. 2.1.1.8) through a ping-pong mechanism using S-adenosyl-L-methionine as cofactor. The tele-methylhistamine ( $\tau$ -MH) produced is a substrate for monoamine oxidase-B

(MAO-B) and semicarbazide-sensitive amine oxidases (SSAOs; E.C. 1.4.3.6), such as diamine oxidase (DAO) and benzylamine oxidase (Bz.SSAO). The aldehyde intermediate is further oxidized by aldehyde dehydrogenase (ALD-DH) to tele-methylimidazoleacetic acid ( $\tau$ -MIAA). In rats, histamine possesses a  $K_m$  value of  $\sim 10 \mu\text{M}$  for HMT yet shows substrate inhibition at 30-60  $\mu\text{M}$ . Several substances inhibit HMT, of which tacrine ( $K_i < 50 \text{ nM}$ ) and metoprine are among the most potent.  $\tau$ -MH also induces product inhibition.

In the oxidative pathway, histamine is oxidized by the SSAOs, particularly DAO and Bz.SSAO, but is a poor substrate for the MAOs. The resultant imidazolacetaldehyde is rapidly converted by ALD-DH to imidazole-4-acetic acid (IAA). IAA induces numerous effects in the CNS where it has been shown to act as both a GABA<sub>A</sub> receptor agonist and a GABA<sub>C</sub> receptor partial agonist. IAA is conjugated with phosphoribosyl-pyrophosphate by the action of imidazoleacetic acid 5'-phosphoribosyl transferase (IPRT) to produce imidazoleacetic acid-ribotide (IAA-RP), a compound that has been shown to behave as a potent ligand at multiple imidazoline binding sites ( $EC_{50} \sim 50 \text{ nM}$ ), in addition to displacing clonidine from its non  $\alpha$ -adrenoceptor binding sites. Immunohistochemical studies have shown that IAA-RP is present in neurons throughout the brain. Both phosphatases and 5'-ecto-nucleotidases can convert IAA-RP to IAA-riboside (IAA-R); preliminary findings suggest a rank order of *in vitro* enzyme activities of alkaline-phosphatase > acid-phosphatase > 5'-ecto-nucleotidase.

Histamine's oxidative products can also be derived from pathways independent of histamine. Thus, L-histidine-pyruvate

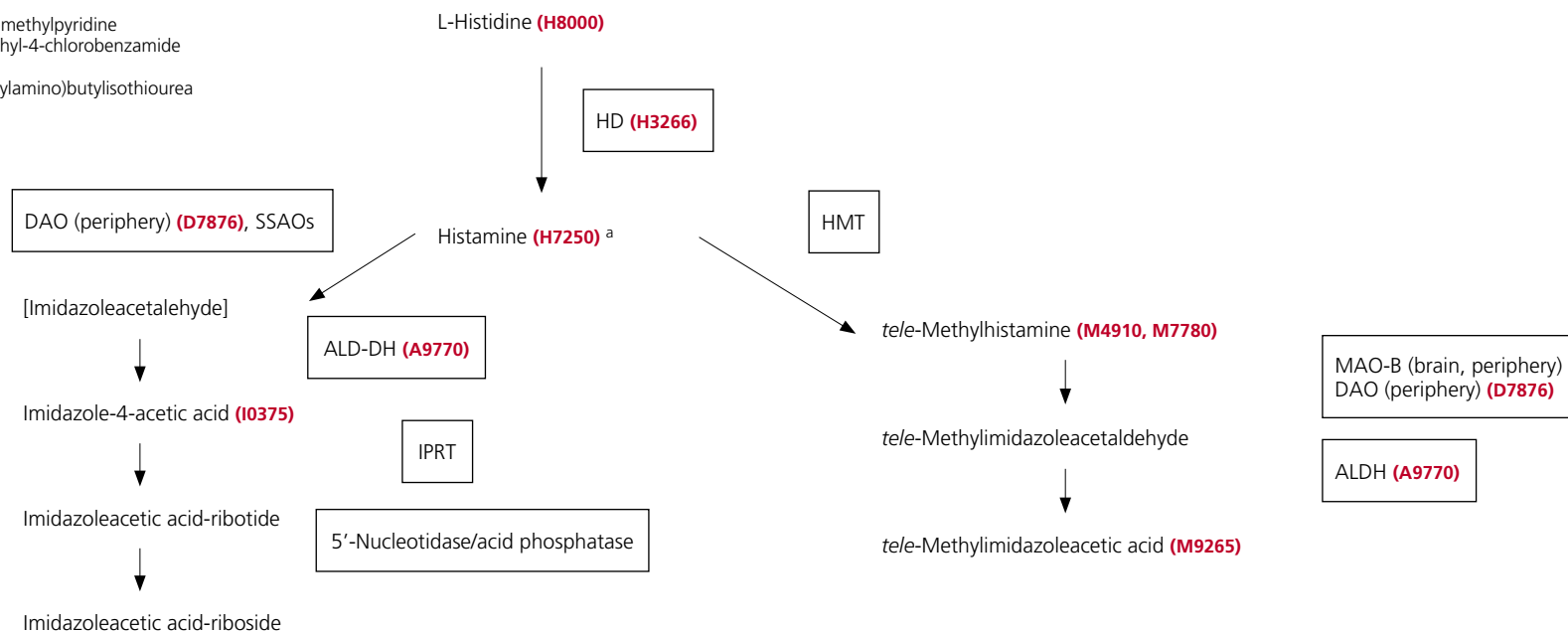
aminotransferase (HPAT), recently termed kyneuramine aminotransferase (KAT) and glutamine transaminase-K (GTK), also leads to IAA production and appears to generate most of the IAA found in brain. In contrast,  $\tau$ -MH and  $\tau$ -MIAA are unique products of histamine metabolism. For example, in plasma and urine of patients with mastocytosis, a state of constant excessive systemic histamine release, levels of histamine may increase only slightly, while levels of  $\tau$ -MH and  $\tau$ -MIAA may increase by as much as 20-fold. Furthermore, because HMT is distal to sites of histamine release, levels of  $\tau$ -MH and  $\tau$ -MIAA together have been used as indices of general histaminergic activity.

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ENZYME	COFACTORS	INHIBITORS
Histidine decarboxylase (HD) (H3266)	Pyridoxal phosphate (P9255)	$\alpha$ -Hydrazinohistidine (H9009), Broscresine, $\alpha$ -Methylhistidine (M8628), $\alpha$ -Fluoromethylhistidine (F134), $\alpha$ -Fluoromethylhistamine
Semicarbazide-sensitive amine oxidases (SSAOs) Diamine oxidase (DAO) (D7876) Semicarbazide-sensitive amine oxidase, benzylamine oxidase (SSAO.BzO)	Oxygen Oxygen	Aminoguanidine (A8835) B24
Aldehyde dehydrogenase (ALD-DH) (A9770)	NAD <sup>+</sup> (N7004)	Cyanamide (C1920), Daidzin (30408), Disulfiram (T1132), Genistin (G0897)
Histamine methyltransferase (HMT)	S-Adenosyl-L-methionine (A7007)	SKF 91488 (S145), Tacrine (A3773), Metoprine
Monoamine oxidase B (MAO-B) (M7441)	Oxygen	Deprenyl (M003), Lazabemide (Ro 19-6327), Pargyline (P8013), Ro 16-6491 (R106)
Imidazoleacetic acid phosphoribosyltransferase (IPRT)	ATP (A2383), PRPP (P8296)	Salicylic acid (S6271)
Acid phosphatase (Acid-P'ase) (P0157)	Mg <sup>2+</sup>	Inorganic phosphate
Alkaline phosphatase (Alk-P'ase) (P5521)	Mg <sup>2+</sup>	Levamisole (L9756), $\beta$ -Glycerophosphate (G6251), Inorganic phosphate
5' Nucleotidase (5'-NTase) (N2779)	Mg <sup>2+</sup>	$\alpha$ , $\beta$ -Methylene-adenosine-5'-diphosphate (M8386), Pentoxifylline (P1784), Inorganic phosphate

## Abbreviations

**B24:** 3,5-Diethoxy-4-aminomethylpyridine  
**Ro 16-6491:** N-(2-Aminoethyl)-4-chlorobenzamide  
**Ro 19-6327:** Lazabemide  
**SKF 91488:** 4-(N,N-Dimethylamino)butylisothiourea



## FOOTNOTES

<sup>a</sup> The propensity for histamine to be methylated (by HMT) or oxidized directly (by DAO or other SSAOs) in mammals varies between species and varies between tissues and organs within species. However, in brains of all mammals, under physiological conditions, histamine is mainly methylated.