

# Histamine Synthesis and Metabolism

## Key References

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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% body stores) and within synaptosomes of certain CNS neurons. When released, histamine induces complex physiological and pathological effects, including immunological reactions, gastric acid secretion, multiple CNS-regulated effects, smooth muscle contraction (e.g. bronchoconstriction) and profound vasodilatation that can lead to cardiovascular collapse.

While in many species pathways of histamine synthesis and metabolism are diverse, 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 nonspecific DOPA decarboxylase (E.C. 4.1.1.26).  $\alpha$ -Fluoromethylhistidine ( $\alpha$ -FMH) is an irreversible, highly selective inhibitor of L-histidine decarboxylase. However, this inhibition often has little or no immediate effect on histamine stores or transmission. 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 only small amounts are oxidized with most being methylated. As a survival mechanism, only traces of histamine escape metabolism, particularly after systemic injection or release, and inhibition of one metabolic route shunts histamine to the other.

Histamine is methylated at the imidazole N furthest from the ethylamine side chain (termed *tele*-N or N<sup>7</sup>) by histamine-N-methyltransferase (HMT; E.C. 2.1.1.8) through a ping-pong mechanism using

S-adenosyl-L-methionine (S-AdoMet) as co-factor. 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). The aldehyde intermediate is further oxidized by aldehyde dehydrogenase (ALDH) to *tele*-methylimidazoleacetic acid ( $\tau$ -MIAA). Histamine-N-methyltransferase is the rate-limiting step. In rats, histamine possesses a  $K_m$  value of  $\sim 10 \mu\text{M}$  for this enzyme, yet shows substrate inhibition at 30-60  $\mu\text{M}$ . Several substances inhibit histamine-N-methyltransferase, of which tacrine ( $K_i < 50 \text{ nM}$ ) and metoprine are among the most potent. In addition,  $\tau$ -MH produces product inhibition.

In the oxidative pathway, histamine is converted to imidazolacetaldehyde by the SSAOs, diamine oxidase, benzylamine oxidase (SSAO.BZO) and possibly others, and is then rapidly converted by ALDH to imidazole-4-acetic acid (IAA). IAA induces numerous CNS-related effects. It is a potent GABA<sub>A</sub> receptor agonist in addition to being a competitive antagonist at native GABA<sub>C</sub> receptors at which it possesses  $\sim 3$ -fold greater affinity than GABA. IAA is conjugated with phosphoribosyl-pyrophosphate (PRPP) (ATP as energy source) by imidazoleacetic acid 5'-phosphoribosyl transferase (IPRT) to produce imidazoleacetic acid-ribotide (IAA-RP). In mammals, the latter exists as the l-4-AA-furanosyl isomer, i.e. the furan ring is linked to the imidazole N furthest from the methylenecarboxy side chain. IAA-RP is a potent ligand at putative imidazoline receptors (e.g. EC<sub>50</sub>  $\sim 50 \text{ nM}$ ), in addition to displacing clonidine from its non  $\alpha$ -adrenoceptor binding sites. Immunohistochemical studies show IAA-RP is

present within neurons in brain where IAA-RP-immunoreactivity exhibits regional specificities related to function. Both phosphatases and 5'-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'-nucleotidase.

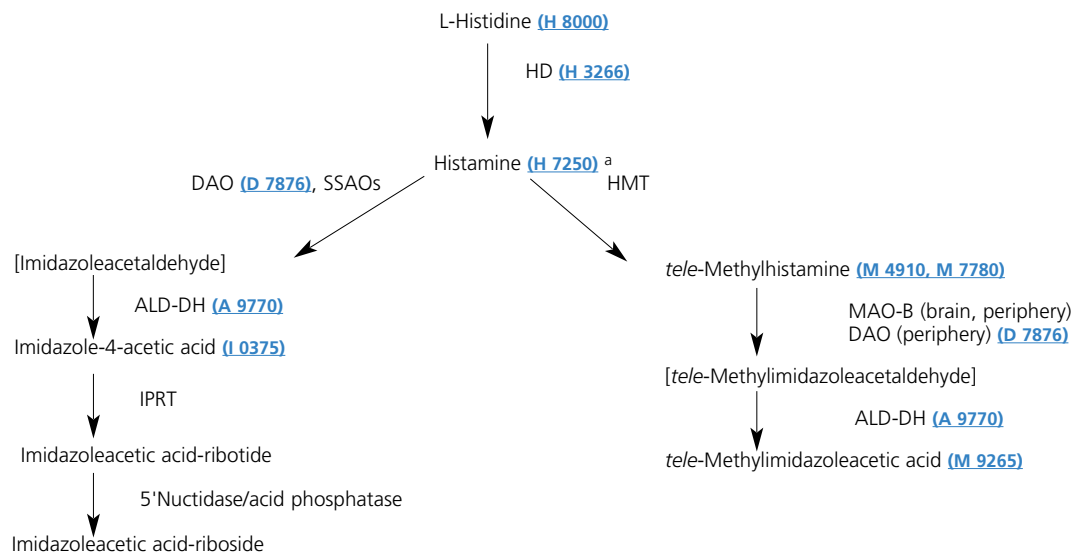
Histamine's oxidative products can also be derived from pathways independent of histamine. L-Histidine aminotransferase (HAT), recently termed kynurenamine aminotransferase (KAT), appears to produce most of the IAA found in brain. In contrast,  $\tau$ -MH and  $\tau$ -MIAA are unique products of histamine 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 its metabolites may increase by as much as 20-fold. 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.

# Histamine Synthesis and Metabolism

ENZYME	COFACTORS	INHIBITORS
Histidine decarboxylase (HD) ( <a href="#">H 3266</a> )	Pyridoxal phosphate ( <a href="#">P 9255</a> )	$\alpha$ -Hydrazinohistidine ( <a href="#">H 9009</a> ), Broscresine, $\alpha$ -Methylhistidine ( <a href="#">M 8628</a> ), $\alpha$ -Fluoromethylhistidine ( <a href="#">F-134</a> ), $\alpha$ -Fluoromethylhistamine
Semicarbazide-sensitive amine oxidases (SSAOs) Diamine oxidase (DAO) ( <a href="#">D 7876</a> ) Semicarbazide-sensitive amine oxidase. benzylamine oxidase (SSAO.Bzo)	Oxygen Oxygen	Aminoguanidine ( <a href="#">A 8835</a> ) B24
Aldehyde dehydrogenase (ALD-DH) ( <a href="#">A 9770</a> )	NAD <sup>+</sup> ( <a href="#">N 7004</a> )	Cyanamide ( <a href="#">C 1920</a> ), Daidzin ( <a href="#">30408</a> ), Disulfiram ( <a href="#">T 1132</a> ), Genistin ( <a href="#">G 0897</a> )
Histamine methyltransferase (HMT)	S-Adenosyl-L-methionine ( <a href="#">A 7007</a> )	SKF 91488 ( <a href="#">S-145</a> ), Tacrine ( <a href="#">A 3773</a> ), Metoprine
Monoamine oxidase B (MAO-B)	Oxygen	Deprenyl ( <a href="#">M-003</a> ), Labzabemide (Ro 19-6327), Pargyline ( <a href="#">P 8013</a> ), Ro 16-6491 ( <a href="#">R-106</a> )
Imidazoleacetic acid phosphoribosyltransferase (IPRT)	ATP ( <a href="#">A 2383</a> ), PRPP ( <a href="#">P 8296</a> )	Salicylic acid ( <a href="#">S 6271</a> )
Acid phosphatase (Acid-P'ase) ( <a href="#">P 0157</a> )	Mg <sup>2+</sup>	Inorganic phosphate
Alkaline phosphatase (Alk-P'ase) ( <a href="#">P 5521</a> )	Mg <sup>2+</sup>	Levamisole ( <a href="#">L 9756</a> ), $\beta$ -Glycerophosphate ( <a href="#">G 6251</a> ), Inorganic phosphate
5'Nucleotidase (5'-NTase) ( <a href="#">N 2779</a> )	Mg <sup>2+</sup>	$\alpha,\beta$ -Methylene-adenosine-5'-diphosphate ( <a href="#">M 8386</a> ), Pentoxifylline ( <a href="#">P 1784</a> ), 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.