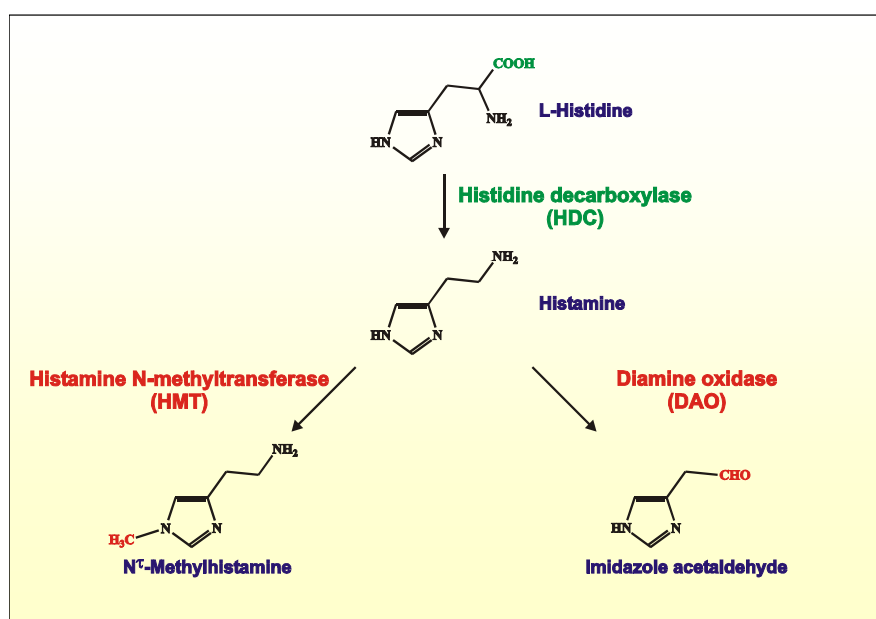


## Metabolism of histamine

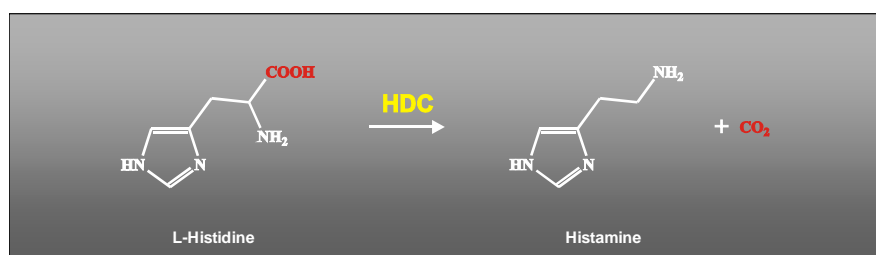
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**Histamine** [2-(4-Imidazolyl)-ethylamine] is an important mediator of many biological processes including inflammation, gastric acid secretion, neuromodulation, and regulation of immune function. Due to its potent pharmacological activity even at very low concentrations, the synthesis, transport, storage, release and degradation of histamine have to be carefully regulated to avoid undesirable reactions. Histamine is also generated by microbiological action in the course of food processing and it is therefore present in substantial amounts in many fermented foodstuffs and beverages.

Histamine is formed by decarboxylation of the amino acid L-histidine in a reaction catalyzed by the enzyme histidine decarboxylase. The major routes of histamine inactivation in mammals are methylation of the imidazole ring, catalyzed by histamine N-methyltransferase, and oxidative deamination of the primary amino group, catalyzed by diamine oxidase<sup>1</sup>.



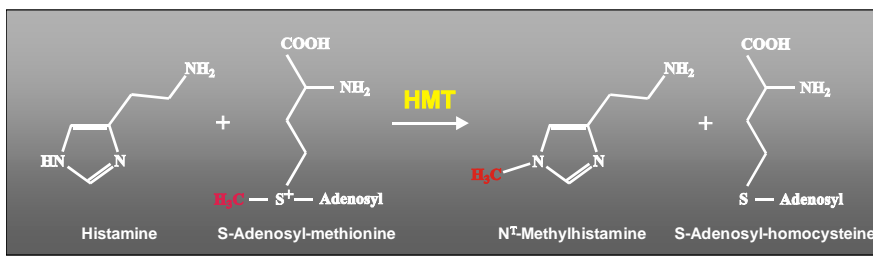
**Histidine decarboxylase** (HDC, EC 4.1.1.22) generates histamine by catalyzing the removal of the carboxyl group from the amino acid L-histidine<sup>2</sup>.



Mammalian HDC enzymes utilize pyridoxal-phosphate as an active-site cofactor. HDC is synthesized as a 74 kDa precursor consisting of 662 amino acid residues that is processed to a 54 kDa active form that apparently forms homodimers. Although the details of HDC processing have yet to be worked out the active enzyme appears to be a cytosolic protein. In mammals, the enzyme is encoded by a single gene with twelve exons designated HDC. The human HDC gene is located on chromosome 15q21-22. HDC is an unstable protein that is synthesized only when a cell needs to make histamine and the

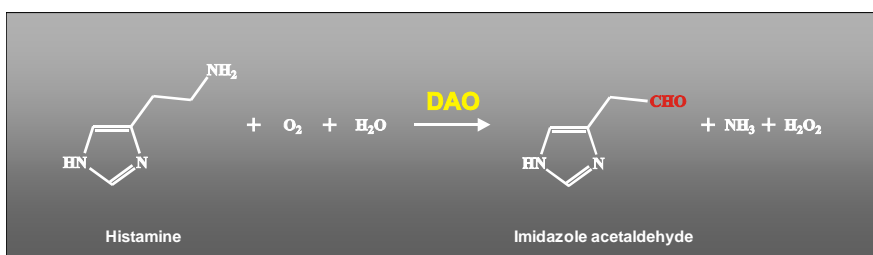
enzyme is immediately degraded when sufficient histamine has been generated. Therefore, HDC is detectable only in cells actively synthesizing histamine. In contrast, the histamine degrading enzymes HMT and DAO are constitutively produced and are present in relatively constant amounts. Mast cells, basophils, enterochromaffin-like cells in the gastric mucosa and histaminergic neurons synthesize considerable amounts of histamine and store the mediator in special storage granula inside the cell. Upon appropriate stimulation, these cells can rapidly release relatively large amounts of histamine and thereby efficiently activate suitable effector mechanisms. In recent years, it became clear that apart from these histamine-storing cell types, many other cells including epithelial cells and lymphocytes can express HDC and synthesize histamine. In these cells, histamine is not stored but appears to be made short-term in small amounts and immediately released. The regulation and function of this low level histamine release is a matter of investigation.

**Histamine N-methyltransferase** (HMT, EC 2.1.1.8) catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to the secondary amino group of the imidazole ring forming N<sup>T</sup>-methylhistamine<sup>3</sup>.



HMT is a small monomeric protein of 29-34 kDa consisting of a single polypeptide chain of ca. 290 amino acid residues. HMT does not appear to carry any modifications and the enzyme does not require any cofactors for its activity. HMT has a two-domain structure with the larger N-terminal domain being a classic methyltransferase fold with an SAM binding motif. Mammalian HMT polypeptide sequences are highly conserved and HMT is encoded by a single gene designated HNMT that has six or seven exons. The human HNMT gene has been mapped to chromosome 2q22.1. HMT is a cytosolic protein that is highly specific for histamine and does not show significant methylation of other substrates. HMT is present in most tissues of mammals but the enzyme is absent from body fluids. HMT is responsible for the inactivation of intracellular histamine that is either synthesized in the cell or taken up from the extracellular space, likely after binding to one of its receptors present on the cell surface. The fact that HMT is ubiquitously expressed indicates that many cells have to deal with histamine, emphasizing the wide-spread role of this mediator.

**Diamine oxidase** (DAO, EC 1.4.3.6) uses molecular oxygen to oxidatively deaminate histamine to imidazole acetaldehyde, ammonia and hydrogen peroxide<sup>4</sup>.



DAO is a member of the class of copper-containing amine oxidases that have in their active-sites a copper ion bound by three conserved histidine residues and the cofactor 2,4,5-trihydroxyphenylalanine quinone, formed post-translationally from a conserved tyrosine residue. Mammalian DAO polypeptide sequences are highly conserved and DAO is encoded by a single gene designated ABP1 or AOC1 that has five exons. The human DAO gene is located on chromosome 7q35. Mammalian DAO is a homodimeric glycoprotein of 200 kDa consisting of two polypeptides of ca. 750 amino acid residues. At the N-terminus, DAO has a signal peptide sequence that targets the protein for secretion. DAO is expressed mainly in intestinal and kidney epithelial cells where the enzyme is stored in secretory vesicles at the basolateral plasma membrane and released into the extracellular space upon stimulation. The best characterised DAO release stimulator is heparin that is released together with histamine by activated mast cells. Apparently, DAO is released locally to inactivate the excess of extracellular histamine to terminate its action. Besides taking care of endogenously released histamine, DAO in the gut is also responsible for catabolizing dietary histamine present in considerable amounts in certain food to prevent its uptake into the circulation. In addition to histamine, DAO also deaminates other diamines with primary amino groups such as 1,4-diaminobutane (putrescine), 1,5-diaminopentane (cadaverine), and agmatine, the decarboxylation product of L-arginine.

As outlined in another section, histamine exhibits its diverse biological actions by binding to and thereby activating four different G-protein coupled receptors that are present at the surface of histamine responsive cells. The primary goal of histamine inactivation is its conversion to metabolites that will not activate histamine receptors and this is achieved either by methylation or by oxidation. The products of the alternative routes of histamine inactivation are further metabolized. N -methylhistamine is oxidatively deaminated to N -methylimidazole acetaldehyde by mitochondrial monoamine oxidases (MAO) and then oxidized by aldehyde dehydrogenases to the N -methylimidazole acetic acid. Imidazole acetaldehyde, the product of the DAO reaction, is also oxidized to imidazole acetic acid by aldehyde dehydrogenase and subsequently ribosylated for efficient transport.

## References

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