

Histamine Receptors

Key References

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Overview

The biogenic amine histamine plays an important role in a variety of pathophysiological conditions. In peripheral tissues, histamine is mainly stored in mast cells and basophils. In allergic conditions, histamine is released from these cells and is responsible for several of the well known symptoms of allergic conditions of the skin and airways. In the gastric mucosa, gastrin-induced histamine release fulfills an important physiological role by stimulating parietal cells to secrete gastric acid. In the CNS, histamine is synthesized in specific neurons that are localized in the tubero-mammillary nucleus of the posterior hypothalamus. These neurons project to all major brain areas and are involved in a variety of important physiological functions, including the regulation of the sleep-wake cycle, food intake, cardiovascular control, regulation of the hypothalamic pituitary adrenal-axis (HPA-axis), learning and memory.

Histamine exerts its action via at least four distinct receptor subtypes. Molecular biological approaches have shown that all histamine receptors belong to the large family of G protein-coupled receptors. The gene encoding the H₃ receptor has only recently been cloned. In contrast to the H₁ and H₂ receptor gene, the H₃ receptor gene contains intronic sequences, leading to the identification of various H₃ receptor isoforms following alternative splicing of the introns. The isoforms show distinct expression patterns and signal transduction mechanisms. Using the H₃ receptor sequence, a new histamine (H₄) receptor was identified 'in silico'. This receptor shows the strongest homology to the H₃ receptor and also recognizes histamine with high affinity.

The H₁ receptor couples mainly to G_{q/11} thereby stimulating phospholipase C,

whereas the H₂ receptor interacts with G_s to activate adenylyl cyclase. The histamine H₃ and H₄ receptors couple to G_i proteins to inhibit adenylyl cyclase, and to stimulate MAPK.

Many potent and selective antagonists for the H₁ and H₂ receptors have been developed as successful anti-allergic or anti-ulcer drugs. Selective agonists are currently also available as pharmacological tools. The H₃ receptor was originally described as an autoreceptor, inhibiting the release of histamine from histaminergic neurons in brain. Recently, it was shown that this inhibitory effect is due to constitutive activity of the H₃ receptor. Evidence suggests that the H₃ receptor regulates the release of several important neurotransmitters (e.g. acetylcholine, dopamine, GABA, norepinephrine, serotonin), both in the peripheral and central nervous systems. Highly potent and selective agonists and antagonists have been developed for the H₃ receptor. These ligands are useful pharmacological tools and are currently being assessed for their clinical potential in allergy, inflammatory disorders, attention deficit hyperactivity disorder, Alzheimer's disease and obesity.

The H₄ receptor is highly expressed in peripheral blood leukocytes and intestinal tissue, making this receptor a potentially interesting target in allergic and inflammatory diseases. The receptor shows high affinity for several H₃ receptor ligands (both agonists and antagonists), but recently the first selective antagonists and agonist have been described.

Because of the availability of many potent and subtype selective ligands for histamine receptor subtypes, good radioligands are available. For the H₁ receptor, the antago-

nist [³H]-mepyramine has been successfully used in many preparations, although binding to cytochrome P450 isoenzymes may mask H₁ receptor binding. For the H₂ receptor, the antagonist [¹²⁵I]-iodoaminopotentidine has recently been developed as a high affinity radioligand. As for the H₁ receptor, an agonist radioligand is lacking. In contrast, agonist and antagonist radioligands are available for the H₃ receptor. Initially, the agonists N^α-methylhistamine and (R)-α-methyl-histamine were developed as tritiated radioligands. Both ligands show high affinity labeling of the H₃ receptor with almost no non-specific binding. Originally described as an antagonist, iodoproxyfan acts as a partial agonist in some H₃ receptor models. The iodinated ligand [¹²⁵I]-iodoproxyfan can therefore also be used as an agonist radioligand. [¹²⁵I]-iodophenpropit, [³H]-GR168320, [³H]-clobenpropit and can all be used as H₃ receptor antagonist radioligands. For the H₄ receptor, [³H]-histamine or [³H]-JNJ7777120 can be used as respectively agonist or antagonist radiolabel.

Histamine Receptors

CURRENTLY ACCEPTED NAME	H ₁	H ₂	H ₃	H ₄
STRUCTURAL INFORMATION	487 aa (human)	359 aa (human)	445 aa (human)	390 aa (human)
SUBTYPE SELECTIVE AGONISTS	2-((3-Trifluoromethyl)-phenyl)histamine ^a , N-Methylhistaprodifen	Amthamine	Immethridine (I1909), N-Methylimmepip	4-Methylhistamine, Clobenpropit (C209), Clozapine (C6305)
SUBTYPE SELECTIVE ANTAGONISTS	(+)-Chlorpheniramine (C4915), Pyrilamine (Mepyramine) (P5514), Triprolidine (T6764)	Cimetidine (C4522), Ranitidine (R101), Tiotidine	Clobenpropit (C209) ^b , Ciproxifan ^c (C6848)	JNJ777120 (J3770)
RECEPTOR SELECTIVE AGONISTS	N ^α -Methylhistamine, Histamine (H7250)	N ^α -Methylhistamine, Histamine (H7250)	Histamine (H7250), N ^α -Methylhistamine, R-α-Methylhistamine (H128), Immepip, Imetit (I135)	Histamine (H7250), N ^α -Methylhistamine, R-α-Methylhistamine (H128), Immepip, Imetit (I135)
RECEPTOR SELECTIVE ANTAGONISTS	Not known	Not known	Thioperamide (T123)	Thioperamide (T123)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _s (increase cAMP)	G _i (decrease cAMP)	G _i (decrease cAMP)
RADIOLIGANDS OF CHOICE	[³ H]-Pyrilamine (Mepyramine)	[¹²⁵ I]-Iodoaminopotentidine	[³ H]-N ^α -Methylhistamine, [¹²⁵ I]-Iodophenpropit	[³ H]-Histamine, [³ H]-JNJ777120
TISSUE EXPRESSION	Lung, vasculature, brain	Heart, stomach, brain	Neurons (CNS, PNS)	Mast cells, eosinophils
PHYSIOLOGICAL FUNCTION	Smooth muscle contraction, food intake, sleep-wakefulness	Gastric acid secretion	Regulation sleep, food intake	Chemotaxis, cognition
DISEASE RELEVANCE	Allergic conditions	Gastric ulcers	Cognitive impairment, obesity	Inflammation?

FOOTNOTES

a 2-((3-Trifluoromethyl)phenyl)histamine and N-methylhistaprodifen are full agonists in the guinea-pig ileum, the standard assay system for H₁ receptors. In other systems, the compound may act as a partial agonist, as is the case for many histaminergic agonists, e.g. impromidine and dimaprit at the H₂ receptor.

b *In vitro*, clobenpropit is one of the most potent H₃ receptor antagonists known at the present time (pA₂ = 9.9). It also displays partial H₄ agonist activity.

c Ciproxifan demonstrates good CNS penetration and is 100 times more potent *in vivo* than clobenpropit. Its activity at human H₃ receptors is 100-fold lower than at rat H₃ receptors and in the same order as at human α₂ receptors.