

# Histamine receptors as drug target: Current and future therapeutics

Atteqa Jawad<sup>1</sup>, Richa Kaushal<sup>1</sup>, Muhammad Sohail<sup>2</sup>, Amna Yaqoob<sup>3</sup>

<sup>1</sup> Department of Pharmacology, Bedfordshire, United Kingdom

<sup>2</sup> Department of Biochemistry, Hazara University, Mansehra, Pakistan

<sup>3</sup> Department of Microbiology, Hazara University, Mansehra, Pakistan

## Author's Contribution

<sup>1</sup> Conception, synthesis, data collection and manuscript writing

<sup>2,3</sup> Data collection and manuscript writing

## Article Info.

Conflict of interest: Nil

Funding Sources: Nil

## Correspondence

Atteqa Jawad

[atteqasafdar3@gmail.com](mailto:atteqasafdar3@gmail.com)

**Cite This article as:** Jawad A, Kaushal R, Sohail M, Yaqoob A. Histamine receptors as drug target: Current and future therapeutics. *JSTMU* 2019; 2(1):31-35.

## A B S T R A C T

Histamine is a neurotransmitter responsible for central regulation of inflammatory reactions. Initial studies were done by Sir Henry Dale in 1993. Histamine acts on its four type of receptors. H1 and H2 are well-established with pharmacological status. H1 receptors are mainly linked with inflammatory responses and developed to mitigate the inflammatory symptoms. While H2 antagonists are established with their role in decreasing basal gastric secretions by decreasing the cyclic adenylyl mono phosphate (cAMP), thus used as therapy line for gastric ulcers. H3 being located centrally imparts its central effects in cognitive functions that are pain, sleep, and memory modulation of neurotransmitters release including, dopamine, acetylcholine, noradrenalin and serotonin. H4 is discovered recently during cloning of H3 and found on immune related cells as, mast cells, T cells and dendrites. Experimental studies are helping in development of more pharmacologically worth drugs that can increase the quality of life.

**Keywords:** Histamine antagonist, inflammatory reactions, neurotransmitter

## Introduction

Histamine was first discovered as an autacoid, which acts as a local hormone which works near the synthesis site for a brief duration unlike endocrine glands.<sup>1</sup> The earlier studies published on histamine and regarding its neurotransmitter properties and inflammatory actions.<sup>2</sup> It is found in blood circulation all over the body but its higher concentrations are found in lungs, skin and gastrointestinal tract. Histamine is a basic amine formed by decarboxylation of histidine, an amino acid, in the presence of decarboxylase enzyme. It is found in mast cells, basophils and as histaminocytes. Histamine is stored in an inactive form in intracellular granules in association with acidic protein and heparin. It is released by exocytosis when allergic stimuli interact with cell surface receptors or antigen IgE interaction with antibody and results in type I inflammatory reaction.<sup>3</sup> When released, it is metabolized either by action of di-amine oxidase DAO and histamine-N-methyl transferase (HNMT). DAO is stored in epithelial cells and released in blood circulation, when required, and is responsible for extracellular histamine metabolism and reducing its effect.

While, HNMT is responsible for the fate of intracellular histamine.<sup>4</sup> Anti-histamine drugs are developed in order to mitigate the inflammatory response, by blocking any of the relevant histamine receptors. Locations and effects of histamine receptors are shown in table 01.

### Histamine receptors as drug targets:

All four types of histamine receptors are specific in their immune responses. The H1 and H2 receptors and their therapeutic uses have been studied in detail, while, H3 and H4 are still under in-depth investigation.

### H1 receptors as drug targets:

H1 receptor histamines were discovered in early 20th century by Swiss-Italian Pharmacologist Daniel Bovet for the relief of allergic symptoms. He won the Nobel Prize for this discovery in 1957. The discovery of H1 Antagonist led to the development of first, second and third generation of histamine antagonists.<sup>5</sup> H1 receptors which are found on mast cells, basophil, eosinophil, when activated by antigen or stimuli binding with receptors lead to the bursting of these cells ultimately resulting in the release of

Inflammatory mediators interleukins, leukotriene, cytokines, and Histamine that then impart their inflammatory actions. H1 receptor antagonist are mainly involved in mitigating the symptoms of nasal congestion, itch, edema, rhinitis airways and skin inflammation.<sup>6</sup>

**Table 1: Location and effects of histamine receptors**

Histamine Receptor	Location by cells	Systemic location	Major effects
H1	Smooth muscles, Endothelial cells, Epithelial cells, Neutrophils Eosinophil Monocytes, Macrophage, T and B cells	Exocrine	Increase mucus secretions
		Respiratory	Bronchiolar constriction Decrease Lung capacity
		Intestinal	Intestinal Cramps Diarrhea
		Skin	Triple response
		Neuromuscular	Itch & pain
		Cardiovascular	Positive Chronotropic, Ionotropism
H2	Parietal cells	Stomach	Increased acid secretion
	Smooth cells	Cardiovascular	Positive chronotropic
H3	Histaminergic neurons	CNS	Cognitive effects Pain, sleep
H4	Mast cells, Eosinophil, T & Dendritic cells	Immune system	Immune response

Following are the different generations of H1 antihistamines:

First generation:

The first generation H1 antagonists are lipophilic and can cross the blood brain barrier (BBB) resulting in CNS effects of marked sedation, increased appetite and weight gain. They are still used because of their high receptor binding ability despite their binding to acetylcholine, serotonin and calcium channels. Decreased alertness and marked sedation are their major side effects.<sup>7, 8</sup>

Second generation:

The histamine antagonists cannot cross Blood Brain Barrier (BBB), thus avoiding the CNS effects. Moreover, these are selective to the H1 receptors avoiding the muscarinic effects. They are potent and efficient than the first-generation drugs. Some of these even have longer duration of action, thus having a competitive advantage over the first generation.<sup>9</sup> However, some of these like terfenadine and astemizole show marked cardiotoxicity leading to market withdrawal. Some of these second-generation histamine antagonists also show somnolence and sedation at high doses.<sup>10</sup>

Current and future findings of H1 antagonist:

Possible third generation:

Apart from the well-established first- and second-generation antihistamines, the second-generation histamine blocker used to relieve nasal congestion and other respiratory inflammation symptoms. Dr. Holgate first introduced, Ebastine, in 2003 which had significant competitive therapeutic profile over the already discovered antagonists. As shown in table 02, but being an inverse agonist is not good alone and need other H1 antagonists in combination for profound pharmacological effect.<sup>11</sup> However, its one metabolite, Carebastine has H1 antagonist property.<sup>12</sup> But according to Consensus group on new-generation antihistamines (CONGA) recommendations and its clinical effectiveness it has the potential to be added in the third generation of H1 antagonist.<sup>13</sup>

H2 receptor drug targets:

H2 receptor antagonists are mainly related to the treatment of gastric ulcer by decreasing the basal and food related acid secretion. H2 antagonist binds to histamine receptors leading to the decrease in cAMP and thus inhibiting the gastric secretion.<sup>14</sup>

Most well-known H2 antagonists include: Cimetidine, Famotidine, Nizatidine, and Ranitidine. Although all of the given H2 antagonists are effective in decreasing basal gastric acid secretions, studies have revealed that Famotidine is 9 and 32 times more potent than Ranitidine and Cimetidine respectively. It has long duration of action

and has been proven safe and effective in long term therapies as in Zollinger-Ellison syndrome.<sup>15</sup>

**Table 2: First- and second-generation antihistamines and their potential advantages and disadvantages**

Advantages	H1 Antagonists	Disadvantages
<b>First Generation</b>		
Use for motion sickness	Diphenhydramine Hydroxyzine	
Long duration of action	Promethazine Cyproheptadine	Appetite & weight gain
<b>Second Generation</b>		
Long duration of action Non-sedating	Fexofenadine	
Non-sedating	Loratidine	Appetite & weight gain
Non-sedating	Cetirizine	
Long duration of action	Astemazole	Slow onset of action Cardiotoxicity
<b>Possible third generation</b>		
Non-sedating No cardiotoxicity No muscarinic effects	Ebastine	H1 inverse agonist

Current findings and future for H2 antagonists:

Long term therapy with H2 antagonist results in development of tolerance against the drug. But in 2010 under the light of research it was suggested that the intermittent administration of H2 antagonist do not cause tolerance.<sup>16</sup>

H3 receptor drug targets:

H3 receptors are present in the histaminergic neurons in small part of the hypothalamus and its axons spread as fine paths throughout the brain,<sup>17</sup> resulting in its effects on CNS. Although histamine in circulation cannot cross the BBB but here histamine acts on histaminergic neurons for its outcomes. Histamine executes its effect through G protein coupled receptors. H3 receptors being involved in negative feedback, self-neurotransmitter release produces histaminergic effects but also involve in modulating effects of other neurotransmitters.<sup>18</sup> Presynaptic effects help in controlled release of Histamine

while postsynaptic modulate the release of other neurotransmitters like acetylcholine and dopamine.<sup>14</sup> H3 plays important role in memory, cognitive functions, sleep, pain, and regulation of normal haemostasis of body and also in a tension deficit hyperactivity disorder (ADHD), Alzheimer’s disease, sleep cycle and obesity.<sup>15, 16</sup>

Acetylcholine modulation:

H3 antagonist enhances the release of acetylcholine while its agonist decreases its release. Thus, use of H3 antagonist has implications in short-term memory impairment.<sup>19</sup>

Dopaminergic modulation:

H3 antagonist also has effect in modulating Dopaminergic release. As observed in Schizophrenia, H3 antagonist modulates release of dopamine and helps treat dopamine imbalance. Hyperdopaminergic, positive schizophrenic symptoms (attention deficiency, apathy) can be targeted by using H3 antagonists.<sup>20</sup> Studies reveal that H3 agonist result in decrease dopamine release but H3 antagonist alone produce no direct effect.<sup>21</sup> However administering H3 antagonist in the presence of Methamphetamine (Amphetamine derivative) can potentiate the dopaminergic effect. H3 antagonist here potentiates the methamphetamine effects centrally showing their effect in CNS.<sup>22</sup>

Norepinephrine modulation:

Norepinephrine, present in cortical and hippocampus regions is responsible for attention and behavioural responses. Many psychotic ailments are modulated by noradrenergic release. H3 receptor antagonists are also here to serve their purpose especially GSK189254\* (H3 antagonist in pre-clinical models), an H3 antagonist increased basal noradrenergic release resulting betterment in cognitive impairment.<sup>13</sup>

Serotonin modulation:

Serotonin is linked with treating unipolar depressions by using Serotonin re-uptake inhibitors. The role of H3 antagonist in Serotonin modulation is different. H3 antagonist increased the release of serotonin in-vitro however the effect was not corroborated by studies conducted in vivo. The action of H3 agonist is observed as the decreasing effect on the release of serotonin in vivo and its effect was successfully conversed by the use of H3 antagonist. Furthermore, alone it has no effect on serotonin release. However, this field can be of good

interest to carry on research for any combination of H3 antagonist and serotonin reuptake inhibitor for serotonin modulation.<sup>8-11</sup> H3 antagonist being a modulator of above, and also Histamine itself is involved in cognitive regulation. Some of the studies reported that its inhibition is effective for smooth cognitive functions. Thioperamide, an H3 antagonist has shown compelling results in improving cognitive functioning.<sup>13</sup>

Future for H3 antagonists:

GSK189254\*, an H3 antagonist that modulates the release of acetylcholine, dopamine and noradrenergic neurotransmitters is under investigation for therapeutic intervention of cognitive impairments. Moreover, Pfizer has more than a dozen applications for patent rights for anti-inflammatory drugs for respiratory inflammation in combination and also CNS effecting drugs.<sup>14</sup> Apart from H3's Central effects H3 receptors are also found peripherally in gastrointestinal system, Respiratory system and cardiovascular system. H3 receptors found in postganglionic region in bronchi are seemed to be effective in asthma therapy as these can prevent bronchoconstriction. Combination of H1 and H3 pharmacophores, thought to be effective in nasal congestion and cutaneous itch, are being designed. GlaxoSmithKline (GSK) developed a ketopiperazine compound, GW-784568X that has passed Phase I/II Clinical trials and applied for its patent right. It is meant for relieving the nasal congestions. Moreover, two other compounds; a combination of H1 and H2 antagonists are also in Phase II of clinical development for relieving allergic rhinitis.<sup>15</sup>

H4 receptor antagonist:

During the cloning of H3 receptor researchers have found that previously discovered G-protein coupled receptor is H4 receptor as responded to the Histamine by decreasing the cAMP production.<sup>21</sup> H4 receptors are found abundantly on eosinophil, monocytes, basophils, dendritic cells, mast cells, and T cells, suggesting its implications in treatment of inflammatory disorders and pruritus.<sup>22</sup>

Current H4 targets and future Aspects:

Studies are being carried out to understand H4 receptor. It is related to itch as H4 agonist clobenprop. It led to pruritus and itch so its antagonizing effect will possibly treat these conditions. One of the standard H4

antagonists JNJ7777120 is used in studies to find out more about H4 receptors. A study carried out to check the anti-inflammatory effects of JNJ7777120 in rat model with carrageenan induced inflammation and thermal hyperalgesia. A 10 to 30 mg/kg subcutaneous administration into the subjects lead to the evident relief of oedema in initial 2 hours along-with it temperature was also moving to normal thus having significant anti-inflammatory and analgesic effect.<sup>23</sup> It has shown experimentally that combination of H1 and H4 antagonist can be worth in developing therapy for murine asthma. Combination of Mepyramine (H1 antagonist) and JNJ7777120 (H4 selective antagonist) has shown synergic effect for treating murine asthma. Furthermore, this experimental study also gives a new sight for study and development either of developing combination drugs of H1 and H4 targets or by one ligand for both receptors or two ligands forming a synergic pharmacophore.<sup>24</sup>

**References**

1. Coruzzi G, Adami M, Guaita E, de Esch IJ and Leurs R. Anti-inflammatory and ant nociceptive effects of the selective histamine H4-receptor antagonists JNJ7777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation. *Eur J Pharmacol* 2007; 563(1-3):240-4.  
DOI: <https://doi.org/10.1016/j.ejphar.2007.02.026>
2. Esbenschade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD and Brioni JD. The histamine H3 receptor: an attractive target for the treatment of cognitive disorders. *Br J Pharmacol* 2008; 154(6):1166-81.  
DOI: <https://doi.org/10.1038/bjp.2008.147>
3. Gemkow MJ, Davenport AJ, Harich S, Ellenbroek BA, Cesura A and Hallett D. The histamine H3 receptor as a therapeutic drug target for CNS disorders. *Drug Discov Today* 2009; 14(9-10):509-15.  
DOI: <https://doi.org/10.1016/j.drudis.2009.02.011>
4. Holgate ST, Canonica GW, Simons FE, Taglialatela M, Tharp M, Timmerman H. et al. This Consensus Group was convened under the auspices of the British Society for Allergy and Clinical Immunology. Consensus group on new-generation antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy* 2003; 33(9):1305-24.  
DOI: <https://doi.org/10.1046/j.1365-2222.2003.01769.x>
5. Howard JM, Chremos AN, Collen MJ, McArthur KE, Cherner JA, Maton PN. et al. Famotidine, a new, potent, long-acting histamine H2-receptor antagonist: comparison with cimetidine and ranitidine in the treatment of Zollinger-Ellison syndrome. *Gastroenterology* 1985; 88(4):1026-33.  
DOI: [https://doi.org/10.1016/S0016-5085\(85\)80024-X](https://doi.org/10.1016/S0016-5085(85)80024-X)
6. Jutel M, Akdis M. and Akdis CA. Histamine, histamine receptors and their role in immune pathology. *Clin Exp Allergy* 2009; 39(12):1786-800.  
DOI: <https://doi.org/10.1111/j.1365-2222.2009.03374.x>
7. Leurs R, Chazot PL, Shenton FC, Lim HD. and De Esch IJ. Molecular and biochemical pharmacology of the histamine H4 receptor. *Br J Pharmacol* 2009; 157(1):14-23.

- DOI: <https://doi.org/10.1111/j.1476-5381.2009.00250.x>
8. Lüllmann H, Mohr K, Hein L. and Bieger D. Color atlas of pharmacology. New York: Thieme; 2000.
  9. Maintz L, "American journal of clinical nutrition," pp. 12-28, 2008.
  10. Mattila MJ, Paa. And kari I. Variations among non-sedating antihistamines: are there real differences?. *Eur J Clin Pharmacol* 1999; 55(2):85-93.  
DOI: <https://doi.org/10.1007/s002280050600>
  11. Medhurst AD, Atkins AR, Beresford IJ, Bracken BK, Briggs MA, Calver AR. et al. GSK189254, a novel H3 receptor antagonist that binds to histamine H3 receptors in Alzheimer's disease brain and improves cognitive performance in preclinical models. *J Pharmacol Exp Ther* 2007; 321(3):1032-45.  
DOI: <https://doi.org/10.1124/jpet.107.120311>
  12. Munzar P, Tanda G, Justinova Z. and Goldberg SR. Histamine h3 receptor antagonists potentiate methamphetamine self-administration and methamphetamine-induced accumbal dopamine release. *Neuropsychopharmacology* 2004; 29(4):705.  
DOI: <https://doi.org/10.1038/sj.npp.1300380>
  13. Howland RD, Mycek MJ, Harvey RA, Champe PC. Lippincott's illustrated reviews: Pharmacology. Philadelphia: Lippincott Williams & Wilkins; 2006.
  14. Nakamura T, Itadani H, Hidaka Y, Ohta M. and Tanaka K. Molecular cloning and characterization of a new human histamine receptor, HH4R. *Biochem Biophys Res Commun* 2000; 279(2):615-20.  
DOI: <https://doi.org/10.1006/bbrc.2000.4008>
  15. Pfizer L, "Tetra hydro naph thyrindine derivative," WIPO, patentscope, Pub no. WO/2007/052124, May 2007.
  16. Rang HP, Dale MM, Ritter JM, and Moore PK, "Pharmacology," *Oxford journals*, pp. 229, 2003.
  17. Rico S, Antonijuan RM. and Barbanoj MJ. Ebastine in the light of CONGA recommendations for the development of third-generation antihistamines. *Journal of asthma and allergy* 2009; 2:73-92.  
DOI <https://doi.org/10.2147/JAA.S3108>
  18. Roberts DJ. A preclinical overview of ebastine. *Drugs* 1996 Jul 1; 52(1):8-14.
  19. Takahashi M. and Katayama Y. Reversal of the tolerance phenomenon by the intermittent administration of a histamine H2-receptor antagonist. *Can J Gastroenterol Hepatol* 2010; 25(9):1493-7.  
DOI: <https://doi.org/10.1111/j.1440-1746.2010.06308.x>
  20. Wagner E, Wittmann HJ, Elz S. and Strasser A. Mepyramine–JNJ7777120-hybrid compounds show high affinity to hH1R, but low affinity to hH4R. *Bioorg Med Chem Lett* 2011; 21(21):6274-80.  
DOI: <https://doi.org/10.1016/j.bmcl.2011.09.001>
  21. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardio toxic actions of terfenadine. *JAMA* 1993; 269(12):1532-6.  
DOI: <https://doi.org/10.1001/jama.1993.03500120070028>
  22. Scadding G. Predicting and Establishing the Clinical Efficacy of a Histamine H 1-Receptor Antagonist. *Clin Drug Investig* 2005; 25(3):153-64.  
DOI: <https://doi.org/10.2165/00044011-200525030-00001>
  23. Li M, Hu J, Chen Z, Meng J, Wang H, Ma X. et al. Evidence for histamine as a neurotransmitter in the cardiac sympathetic nervous system. *Am J Physiol Lung Cell Mol Physiol* 2006; 1.  
DOI: <https://doi.org/10.1152/ajpheart.00939.2005>