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Review Article

A Review on Current Research on H3 and H4 Receptors

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A B S T R A C T

This review article provides an overview of the structure, location, and functional uses of H3 and H4 histamine receptors. It examines the current research on the topic, including the structure of the receptors, their location in the body, and their role in the body's response to histamine. It also looks at potential, therapeutic applications of these receptors and their potential to be used as drug targets. The article concludes with a discussion of potential future directions for research on these receptors. The identification of Histamine (H3) & (H4) receptors .Some years ago relined interest in histamine research and exposed attracting perspectives for the potential therapeutic exploitation & these new drug targets. While the H3 receptors is mainly localized in the CNS, the of the brain and the morphologic characterization histamine producing neurons proved the existence of histaminergic system in the mammalian brain, It is primarily expressed in hematopoietic cell, indicating their function in neurotransmission and immunomodulation, respectively. Although structural similarities between H3 and H4 & Species difference in their pharmacological profiles are causes of limitation in their evaluation & their biological profile the development of selective ligands for there receptors. The H3 and H4 is recognised drug target for neuronal diseases, such as Cognitive Disorder, Neuropathic pain and Sleep Wake Disorder considering the topicality & this area of research. This review focuses on the pharmacology of selected promising indication and the rationalefor the application of H3and H4 ligands.

Key Words: H3 Receptor, H3 Antagonist, H4 Receptor, H4 Antagonist, Histamine, Histaminergic Neuron, Anti histamines

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INTRODUCTION

The histamine H_3 receptor (H_3R) was discovered in 1983 and was one of the last receptors that were discovered using conventional pharmacological methods. Its structure was discovered later as a part of an effort to identify a commonly expressed G-protein-coupled receptor (GPCR) in the central nervous system.Gprotein-coupled receptors (GPCRs), also known as seven-(pass) transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptors, and G protein-linked receptors (GPLR)[1]. Pharmacologyis a branch of medicine, biology and pharmaceutical sciences concerned with drug or medication action, where a drug may be defined as any artificial, natural, or endogenous (from within the body) molecule which exerts a biochemical or physiological effect on the cell, tissue, organ, or organism (sometimes the word *pharmacon*and exogenousbioactive species)[2-4]. In 1910, Sir Henry Dale and colleagues (Dale and Laidlaw, 1910) isolated histamine from ergot and later found that it had a stimulant effect on smooth muscle from the gut and the respiratory tract, caused vasodepression, stimulated cardiac contractility, and induced a shock-like syndrome when injected into animals. In 1920, Popielski demonstrated that histamine stimulated gastric acidsecretion, and in 1927, the amine was isolated from the liver and the lung, evidencing that it was a natural constituent of the body.[5-6]

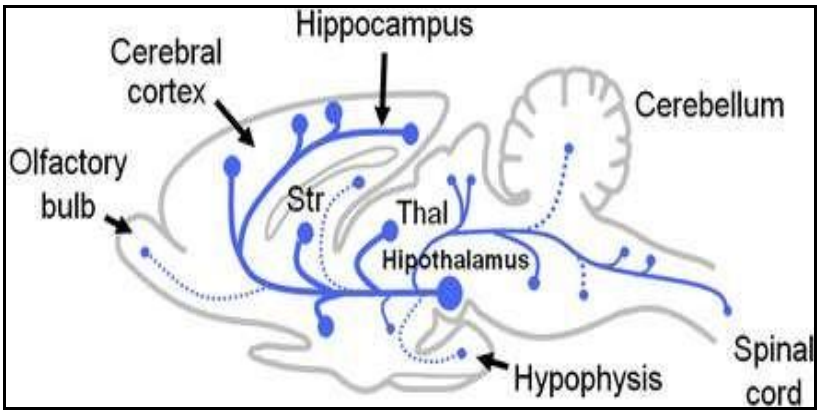

Figure 1: Histaminergic system in the mammalian brain

Although histamine was detected in the brain in 1919 by John J. Abel, its role as a neuromodulator became evident only several decades later; using antibodies against the amine and its synthesizing enzyme, histidine decarboxylase (HDC), the morphologic characterization of histamine-producing neurons proved the existence of a histaminergic system in the mammalian brain in (fig .1)[7-8]

INTRODUCTION OF H4 RECEPTOR

There are now four known G-coupled protein receptors (GPCRs) that use histamine as a ligand. Thesereceptors were discovered over a span of almost 100 years and each discovery provides excellent examples of the use of state-of-the-art receptor pharmacology to discovery new receptors[9]The first actions of histamine were noted around 1910, but this before the idea of receptors was widely accepted. After the development of compounds that blocked the effect of histamine in the 1930–1940s, it was noted that their effects were consistent with a competition for binding at a receptor now known as the histamine H1 receptor [10]

These first antihistamines became the basis for very successful drugs, some of which are still in use today.

However, they also revealed new questions since there were actions of histamine that were not blocked by these ligands. This led to the proposal that a second histamine receptor existed, and the discovery of selective ligands for this receptor led to its pharmacological characterization and the designation as the H2R.[11]A similar story exist for the discovery of the H3R, where it was noted that various histamine receptor ligands modulated histamine actions in the brain, but that the pharmacology did not match the known H1R and H2R [12]Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous short-acting biogenic amine synthesized from the basic amino acid histidine through the catalytic activity of the ratelimiting enzyme histidine.[13]The pharmacological study of histamine started concurrently with its discovery by Sir Henry H Dale at the beginning of the 20th century One of the first described functions was its ability to mimic anaphylaxis and has since been demonstrated to play a major role in inflammatory processes.Following the recognition of its 'somewhat complicated action' byhistamine has been one of the most studied substances in medicine for nearly a century, possessing a wide spectrum of activities (Fig 2) including its potent mediator role in immediate hypersensitivity reactions.[14]

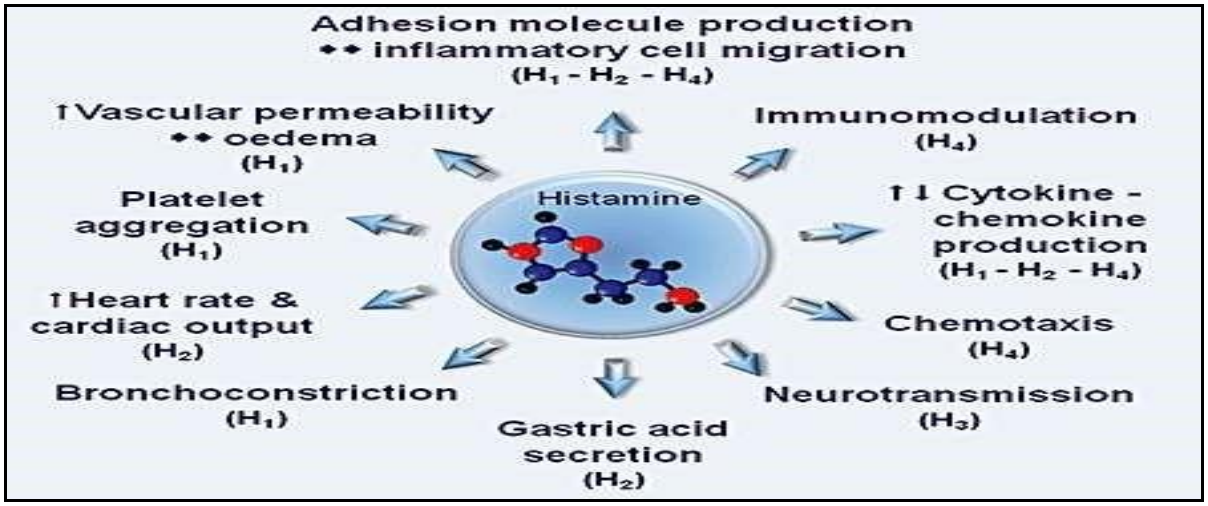

Figure 2: The role of histamine in immune and inflammatory

STRUCTURE AND LOCATION OF H3 RECTOR

The histamine H3 receptor was initially identified as a presynaptic autoreceptor controlling histamine release and synthesis in the brain. histamine H3 receptors are mainly located presynaptically on the postganglionic sympathetic nerve fibers innervating the blood vessels and the heart. Their activation leads to the inhibition of noradrenaline release and consequently to the reduction of the neurogenic vasopressor and cardio stimulatory responses. The presence of such receptors has been shown both in vitro (human, pig, guinea-pig, rabbit, rat isolated tissues) and in vivo (rat, guinea-pig)[21].Histamine H3 receptors are expressed in the central nervous system and to a lesser extent the peripheral nervous system, where they act as autoreceptors in presynaptic histaminergic neurons and control histamine turnover by feedback inhibition of histamine synthesis and release. The H3 receptor has also been shown to pre synaptically inhibit the release of a number of other

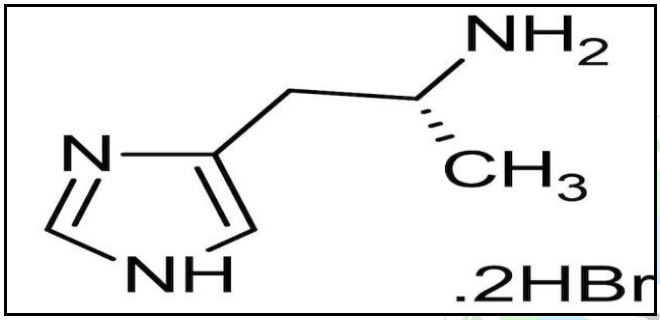

Figure 3: (R)-alpha-methylhistamine

Histamine H3 receptors act as presynaptic auto-receptors that inhibit the synthesis 12 and release of histamine in the histaminergic neurons in the central nervous system (CNS). They also occur as hetero-receptors on neurotransmitters (i.e. it acts as an inhibitory heteroreceptor)Histamine H3 receptors are involved in the pathogenesis of norepinephrine (NE) overflow in myocardial ischemia. H3 receptor agonists (such as imetit) have been shown to attenuate carrier-mediated NE release in models of protracted myocardial ischemia; this is accomplished through a diminished activity of the Na+/H+ exchanger[23-24]Schwartz (1975) and his colleagues also studied histamine release from cerebral neurons in rat cortex. They discovered that histamine could inhibit its own release, and they used H1 and H2 antagonists to characterize the receptor involved. This effect was competitively inhibited by burimamide at nano - molar concentrations. in 1983, the possibility of a H3 receptor. Their suggestion was confirmed and the receptor definitively characterized in 1987 by their discovery that (R)-a-methylhistamine was a potent agonist (chirally selective since the S - isomer is much less potent) and that thioperamide (Figure 2) was a very specific competitive antagonist[24]

nonhistaminergic neurons, modulating the release of other neurotransmitters such as 5-hydroxytryptamine, dopamine, acetylcholine, nor- adrenaline and GABA in the CNS and periphery. Ligands for the H3 receptor have been reviewed.[25-26]Histamine H3 receptor can act either as an autoreceptor or as a heteroreceptor.Ahistamine H3 autoreceptors are located presynaptically in histaminergic neurons where they control both the synthesis and release of histamine from L-histidine. B: histamine H3 heteroreceptors are located presynaptically in non-histaminergic neurons where they control the release of the respective neurotransmitter. L-his: L-histidine; HA: histamine; NT: neurotransmitter; NA: noradrenaline; Acetylcholine; NANC: non-adrenergic-non cholinergic; 5HT: serotonin; DA: dopamine; R: receptor. Activation of H3 receptors inhibits the release of noradrenaline in rat hypothalamus and cortex was reported in the early 90s.

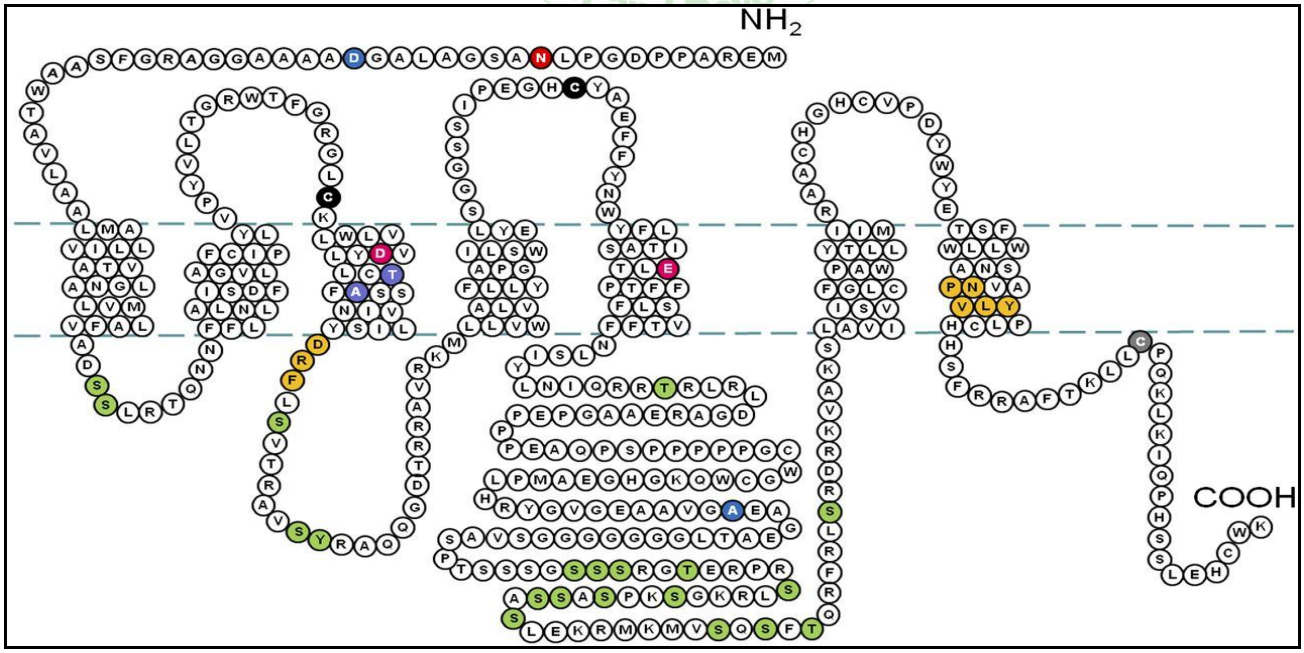

Figure 4: Strucure of human H3R receptor

STRUCTURE AND LOCATION OF H4 RECEPTOR:

The role of H4 receptors in the nervous system is poorly understood. H4 receptors are known to be coupled to Giproteins, and their downstream pathways are postulated to be similar to those described for H3 receptors (Figure 3). Compared to the other three types of histamine receptors, the H4 receptor is not expressed abundantly in the CNS and PNS [15,16] By quantitative single-cell Ca^{2+} imaging, it was demonstrated that histamine induces a Ca^{2+} increase in a subset of sensory neurons (3–10%) via activation of the H1 and H4 receptors as well as inhibition of the H3 receptor. It is assumed that the decreased threshold in response to H3 receptor antagonism, which accounts for the analgesic effect of H3 receptor antagonists, activates H1 and H4 receptors on sensory neurons, which in turn results in the excitation of histamine-sensitive afferents and, therefore, may result in a modulation of pain sensitivity.[17]

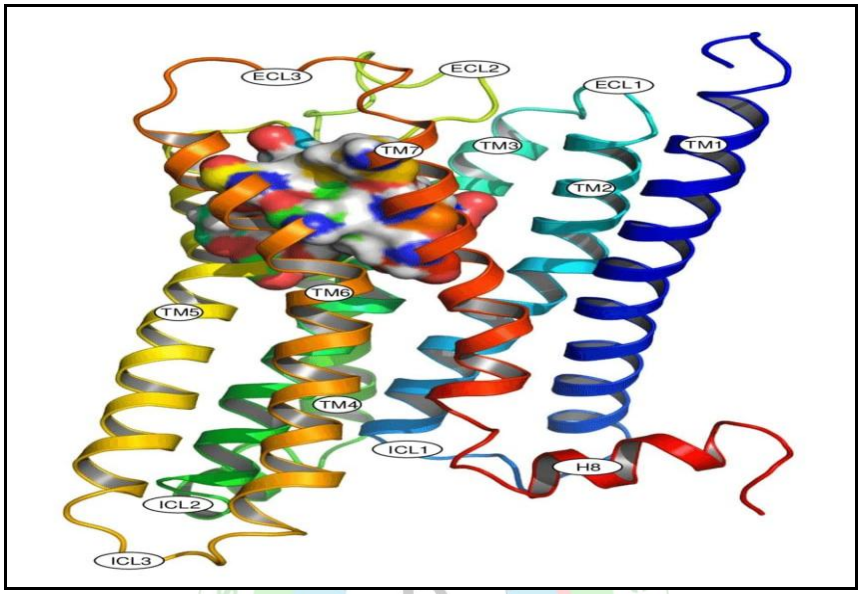

Figure 5: Structure of human histamine H4R

The H4 receptor, which has low homology with other histamine recep- tors, can be primarily found in bone marrow, intestinal tissue, spleen, thymus, and also in various immune cells, such as T cells, mast cells, neutrophils, and eosinophils, showing modulatory effects on these cells, including activation, migration, and production of cytokines and chemokines, suggesting its principal role in the regulation of immune/inflammatory mechanisms.[18,19] Interestingly, recent reports also indi- cate the presence of H4 receptors on peripheral sensory nerves, in the DRG, with more intense staining of small- and medium-diameter cells, and in the spinal cord, especially laminae I and II. This neuronal localization supports H4 receptors involvement in the regulation of neuronal function related to the modulation of nociceptive transmission [20]

USES AND FUNCTIONS OF H3 AND H4 RECEPTORS

Presynaptic Effects

The H3 receptor is known for the Presynaptic regulation of neurotransmitter release in peripheral and CNS nervous system Histamine, Noradrenaline, Dopamine,Acetylcholine(Ach), Glutamate, Serotonin(5HT) And GABA,Neuropeptides this Drug regulates the Presynaptic EffectsH3R for direct action is consistent for these neurotransmitter it is exception for Ach and dopamine[28]

Postsynaptic Effects

It effects in the some areas of the brain,namely as striatum,cerebral

Histamine H3 receptor[29-30]

Histamine function are useful in CNS. CNS have been highly effects on medicated via H3 receptor signaling.Histamine H3 antagonist receptor antagonist is effective for excessive daytime sleepiness in patients with narcolepsya chronic sleep disorder affects overwhelming daytime drowsiness.Histamine H4 receptor are in using in implications in neuronal functions and functional expression of H4 receptors on human and rodent neurons.

Effects of Histamine derivatives on forskolin induced camp accumulation in H3R and H4R

Histamine is effective at a maximum concentration that strongly inhabited camp formation in H3R cells and that all induced in the same maximal inhibition of forskolin induced camp accumulation shows that they all act as full agonists at the H3R.

Histamine receptors as new CNS Drug Targets

Sleep Wake Disorder

Nonimidiazole inverse agonist is known as H3 receptor and that mostly reduced EDS in narcoleptic patients and currently its shows the effective treatment against Parkinson's disease also use in treatment of narcolepsy.

Cognitive Disorder

A current condition phase II clinical trial aims to evaluate the cognitive enhancing effects of the H3 receptor antagonist GSK-239512 in patients along with mild symptoms to moderate Alzheimers disease.

Neuropathic pain

H3 receptor is novel selective as antagonists/ inverse agonist such as GSK-189254 and GSK-334429 are significantly use in surgically induced and virally induced rat models of neuropathic pain.

H3-ANTAGONIST DRUG AVAILABLE IN MARKET

An H3 receptor antagonist is a classification of drugs used to block the action of histamine at H3 receptor. Examples of H3-antagonist drugs include

1) Ciproxifan
2) Betahistine
3) Pitolisant
4) Conessine
5) Clobenpropit
6) Bavisant
7) Viloxazine
8) Proxyfan
9) Iodophenpropit
10) Cipralisant
11) Iodoproxyfan
12) Thioperamide

CIPROXIFAN

Ciproxifan [*cyclopropyl 4-(3-(1H-imidazol-4-yl)propyloxy)phenylketone*]is an extremely potent histamine H3 antagonist. It is a well investigated histamine H3 receptor inverse agonist / antagonist showinghigh specific affinity at rodent as compared to human H3R [31]. Ciproxifan blocksH3 receptor and consequently allow more histamine to be released and have alertness promoting effect. It has been proposed as a potential treatment for sleep disorders such as narcolepsy, to improve vigilance in old age, particularly in the treatment of conditions such as Alzheimer's disease [32]. It also potentiated the effects of anti-psychotic drugs and has been suggested as an adjuvant treatment of Schizophrenia It is also tested in animals model for schizophrenia, sleeping disorders or most recently autism [33].

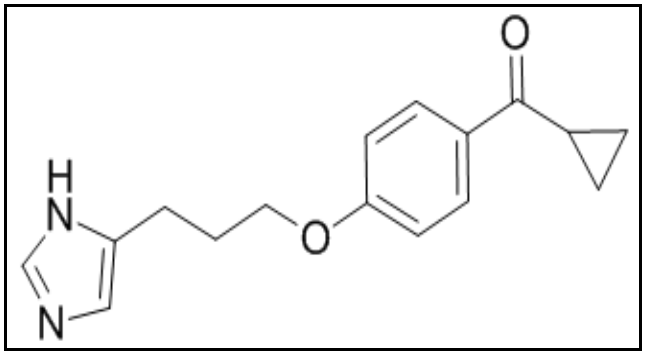

Figure 6: Ciproxifan structure

BETAHISTINE

Betahistine [*2-[2-(methylamino)ethyl]pyridine*] is a structural analogue of histamine that acts as a weak partial post synaptic histamine H1 agonist and presynaptic His receptor antagonist with no effect on post synaptic H_2 receptor [34]. Betahistine is formulated as the dihydrochloride salt. It chemically resembles phenethylamine and histamine. Betahistine is a histamine like anti-vertigo drug used for treating symptoms associated with meniere's disease. H3 antagonism elevates level of neurotransmitters including serotonin in the brainstem, inhibiting the activity of vestibular nuclei, restoring proper balance and decreasing vertigo symptoms. It is metabolized primarily into the inactive metabolite 2- pyridylacetic acid [35]. Betahistine drug available in market as Betavest, Vertin, Vertistar, B-vest, Betahist forte.

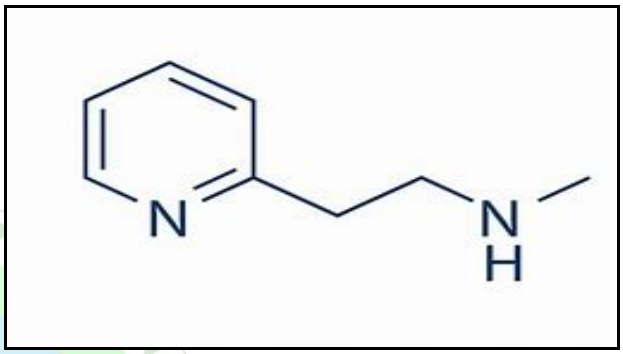

Figure 7: Betahistine structure

PITOLISANT

Pitolisant (wakix) [*1- {3- [3- (4-Chlorophenyl)propoxy]propyl}piperidine*] is a first in class H3R antagonist / inverse agonist which received initial approval in the United States in 2019 for the treatment of EDS in patients with narcolepsy [36]. (EDS: Excessive Daytime Sleepiness). It represents the first commercially available medicine in its class. It enhance the activity of histaminergic neurons in the brain that function to improve a person's wakefullness. Pitolisant is primarily metabolized by CYP2D6 and to a less extent by CYP3A4 in the liver [37].

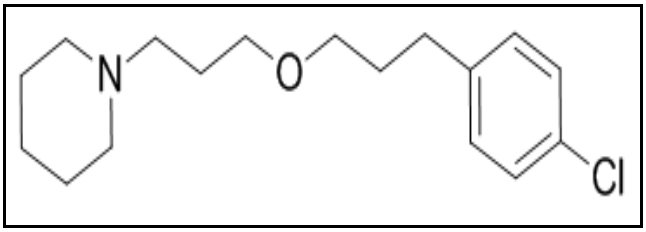

Figure 8: Pitolisant Structure

CLOBENPROPIT

Clobenpropit [1- {3- [3- (4-Chlorophenyl) propoxy] propyl}piperidine hydrochloride] is a histamine H3 receptor antagonist, neuroprotective effects via stimulation of GABA release in brain cells in vitro [38]. The anticonvulsant activity of clobenpropit an isothiourea derivative of histamine and potent H_3 antagonist was investigated in representative seizure models in mice. It enhances GABA release to protect against NMDA-induced excitotoxicity

through the CAMP / protien kinase A pathway in cultured cortical neurons [39].

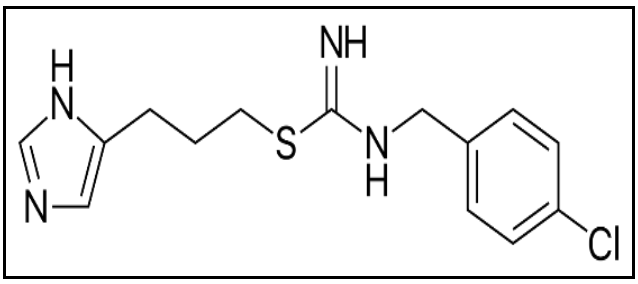

Figure 9: Clobenpropit Structure

BAVISANT

Bavisant has been used in trials studying the basic science and treatment of Alcoholism, Pharmacokinetics, Drug Interactions, Attention Deficit Hyperactivity Disorder, and Attention Deficit Disorders with Hyperactivity Bavisant is an orally active, potent,brain-penetrating and highly selective antagonist of the histamine H3 receptor [40]. Bavisant can be used for attention-deficit hyperactivity disorder (ADHD) research.

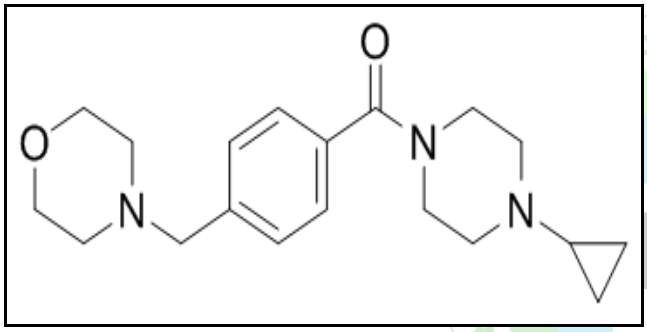

Figure 10: Bavisant Structure

VILOXAZINE

Viloxazine, sold under the brand name Qelbree and formerly as Vivalan among others, is a noradrenergic medication which is used in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults [41]. Viloxazine was first described by 1972 and was marketed as an antidepressant in Europe in 1974. It was not marketed in the United States at this time. Side effects of viloxazine include insomnia, headache, somnolence, fatigue, nausea, vomiting, decreased appetite, dry mouth, constipation, irritability, increased heart rate, and increased blood pressure [42]. Viloxazine is available for ADHD in the form of 100, 150, and 200 mg extended-release capsules. These capsules can be opened and sprinkled into food for easier administration.

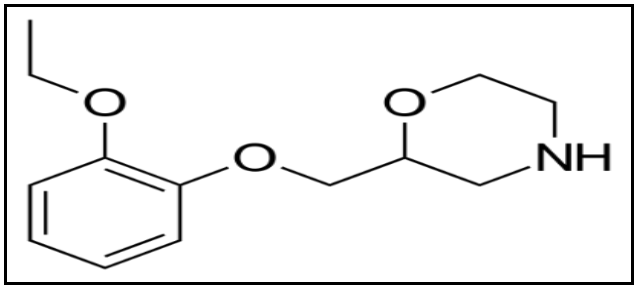

Figure 11: Viloxazine structure

PROXYFAN

Proxyfan [*4-[3-(Benzyloxy)propyl]-1H-imidazole*] is a histamine H3 receptor ligand which is a "protean agonist", producing different effects ranging from full agonist, to antagonist, to inverse agonist in different tissues, depending on the level of constitutive activity of the histamine H3 receptor [43]. It is a histamine H3 receptor protean agonist that can produce a spectrum of pharmacological effects including agonist, inverse agonist, and antagonist. We have discovered that proxyfan (10 mg/kg orally) significantly improved glucose excursion after an IP glucose tolerance test of either lean or high-fat/cholesterol diet-induced obese mice. It also reduced plasma glucose levels comparable to that of metformin (300 mg/kg orally) in a nongenetic type 2 diabetes mouse model.

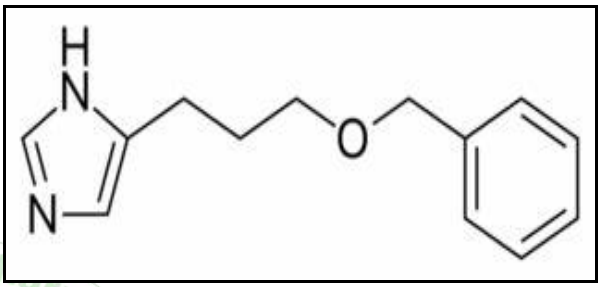

Figure 12: Pyroxyfan Structure

IODOPHENPROPIT

Iodophenpropit [*3-(1H-imidazol-5-yl)propyl N'-[2-(4-iodophenyl)ethyl]Imidothiocarbamate*] is a histamine antagonist which binds selectively to the H3 subtype. Its 125I radiolabelled form has been used for mapping the distribution of H3 receptors in animal studies [44].The H(3) receptor inverse agonist, thioperamide, potently reduced appetite without adverse behavioural effects. This action was blocked by proxyfan, acting as a neutral antagonist in this model and, therefore, this compound is useful in determining the selectivity of H(3) receptor-directed drugs.

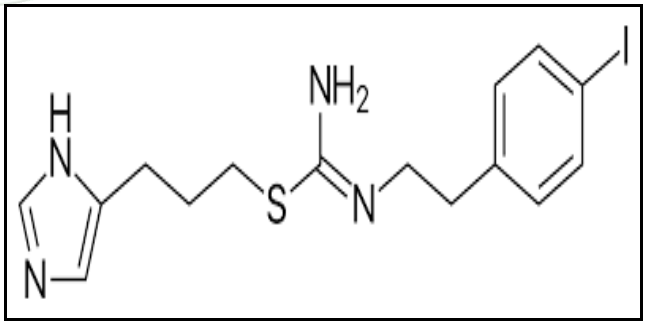

Figure 13: Iodophenpropit Structure

CIPRALISANT

Cipralisant [*5-[(1S, 2S)-2-(5, 5-dimethylhex-1-ynyl) cyclopropyl]-1H-imidazole*] also known as Perceptin, is a highly selective histamine H3 receptor antagonist that was being developed by Gliatech in the US [45]. It is tentative trade name (Perceptin) is an extremely potent histamine H3 receptor ligand originally developed by Gliatech. Cipralisant was initially classified as a selective H3 antagonist, but newer research (2005) suggests also agonist properties, i. e. functional selectivity.Cipralisant seemed to be well tolerated

during early testing, entering Phase II trials for ADHD in 2000.

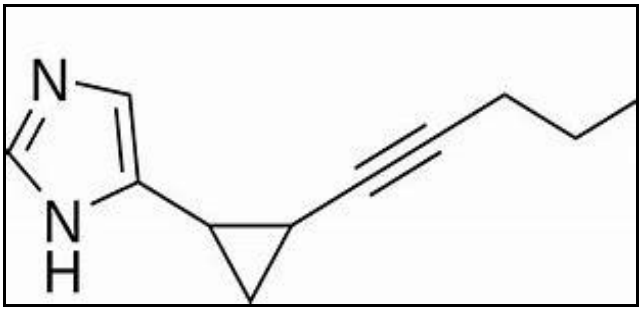

Figure 14: Cipralisant Structure

IODOPROXYFAN

Iodoproxyfan[*3-(1H-imidazol-4-yl)propyl-(4-iodophenyl)-methyl ether*] is a novel potent and selective histamine H3 receptor antagonist [45]. Iodoproxyfan binding to membranes of the rat striatum was reversible and saturable. The specificity of Iodoproxyfan binding to H3 receptors was demonstrated by its pharmacological profile. A series of H3 receptor agonists inhibited iodoproxyfan binding with a similar maximal effect and with the expected order of potency and stereoselectivity ratio.

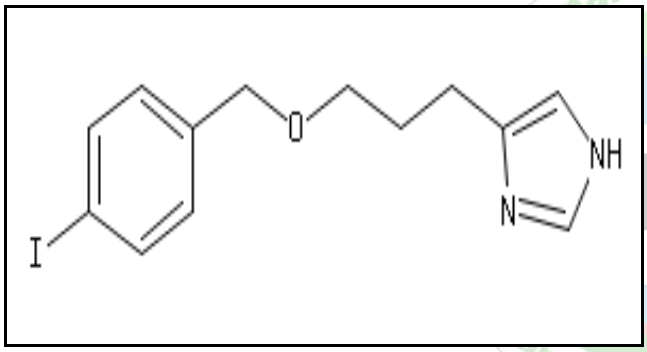

Figure 15: Iodoprxyfan Structure

THIOPERAMIDE

Thioperamide [*N-Cyclohexyl-4- (1H-imidazol-4-yl)-1-pipéridine carbothioamide*] is a potent Histamine H4 antagonist and selective Histamine H3 antagonist capable of crossing the blood–brain barrier. It was found to be an antagonist of histamine autoreceptors, which negatively regulate the release of histamines and enhances the activity of histaminergic neurons by blocking autoreceptors and leading to greater release of histamine [47]. It was used by Jean-Charles Schwartz in his early experiments regarding the H3 receptor. Its action on H_3 is thought to promote wakefulness and improve memory consolidation.

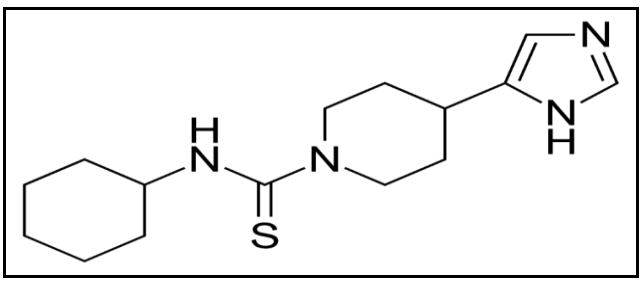

Figure 16: Thioperamide Structure

REFERENCES

1. Yoneyama H, Shimoda A, Araki L, Hatano K, Sakamoto Y, Kurihara T, Yamatodani A, Harusawa S. Efficient approaches to S-alkyl-N-alkylisothioureas: syntheses of histamine H3 antagonist clobenpropit and its analogues. J Org Chem. 2008; 21:96-104.
2. Ligneau X, Lin J, Vanni-Mercier G, Jouvet M, Muir JL, Ganellin CR, Stark H, Elz S, Schunack W, Schwartz J. Neurochemical and behavioral effects of ciproxifan, a potent histamine H3-receptor antagonist. J Pharmacol Exp Ther. 1998; 287(2):658-66.
3. Esbenshade TA, Fox GB, Krueger KM, Baranowski JL, Miller TR, Kang CH, Denny LI, Witte DG, Yao BB, Pan JB, Faghih R, Bennani YL, Williams M, Hancock AA "Pharmacological and behavioral properties of A-349821, a selective and potent human histamine H3 receptor antagonist". Biochemical Pharmacology.2004; 68(5):933-945.
4. WybrzeżeWyspiańskiego,"Pharmacology" Online Etymology Dictionary. Archived from the original,J.Wrocław University of Science and Technology.2017; 27:50-370
5. Airaksinen MS, Panula P. The histaminergic system in the guinea pig central nervous system: an immunocytochemical mapping study using an antiserum against histamine. J Comp Neurol.1988; 273(2):163-86.
6. Alves-Rodrigues A, Leurs R, Willems E, Timmerman H. Binding of clozapine metabolites and analogues to the histamine H3 receptor in rat brain cortex. Arch Pharm (Weinheim).1996; 329(8-9):413-6.
7. Anichtchik OV, Huotari M, Peitsaro N, Haycock JW, Männistö PT, Panula P. Modulation of histamine H3 receptors in the brain of 6-hydroxydopamine-lesioned rats. Eur J Neurosci.2000; 12(11):3823-32.
8. Akdis, C. A., Akdis, M., Bieber, T., Bindslev-Jensen, C., Boguniewicz, M., Eigenmann, P., et al. Diagnosis and treatment of atopic dermatitis in children and adults: European academy of allergology and clinical immunology/American academy of allergy, asthma and immunology/PRACTALL consensus report. J. Allergy Clin. Immunol. 2006; 61(8):969-87
9. Altenbach, R. J., Adair, R. M., Bettencourt, B. M., Black, L. A., Fix-Stenzel, S. R., Gopalakrishnan, S. M., et al. Structure-activity studies on a series of a 2aminopyrimidine-containing histamine H4 receptor ligands. J. Med. Chem. 2008 ;51(20):6571-80
10. Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature.1983; 302(5911):832-7.
11. Aldesic M, Verdrengh M, Bokarewa M, Dahlberg L, Foster SJ and Tarkowski A. Histamine in rheumatoid arthritis. Scandinavia Journal of Immunology.2007; 65(6):530-537
12. Cezmi A, Estelle F and Simons R. Histamine receptors are hot in immunopharmacology. European Journal of Pharmacology.2006; 69-76
13. Bassam BD, Cecilia BB, Henry JE, Ying W and Azzam AM. Functional expression of H4 histamine receptor in human natural killer cells, monocytes, and dendritic cells. The Journal of Immunology. (2007); 179(11):7907-7915)
14. Franco HF, Detlef Z and Bernhard FG. The 21st century renaissance of the basophil? Current insights into its role in allergic responses and innate immunity. Experimental Dermatology. (2006); 15(11):855-864.
15. Malinowska R, Godlewski G and Schliker E. Histamine H3 Receptors – General Characterization and their function in the cardiovascular system. Journal of Physiology and Pharmacology.1998; 191-211
16. Randi BS, Christina JM, Neil S, Irina LK, Kara L, Timothy LW, and Roberto L. Coupling of histamine H3 receptors to neuronal Na+/H+ exchange: A novel protective mechanism in myocardial ischemia. Proceedings of the National Academy of Sciences.2001; 98(5):2855-2859.
17. Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature.(1983); (302: 832-837)
18. Arrang JM, Garbarg M, Lancelo JC, Lecomte JM, Pollard H, RobbaM, Schunack W and Schwartz JC. Highly potent and selective ligands for histamine H3-receptors. Nature.(1987); (117-123)

19. Mike EP & Robin GC. Histamine and its receptors. Brirtish Journal of Pharmacolgy. (2006); (S127-S135)
20. Arrang JM, Garbarg M, Lancelo JC, Lecomte JM, Pollard H, RobbaM, Schunack W and Schwartz JC. Highly potent and selective ligands for histamine H3-receptors. Nature Journal.(1987); (117-123)
21. R E West Jr , A Zweig, N Y Shih, M I Siegel, R W Egan, M A Clark,Identification of two H3-histamine receptor subtypes,J.Molecular Pharmacology..(1999); 38(5):610-3
22. Gustavo Nieto-Alamilla , Ricardo Márquez-Gómez , Ana-Maricela García-Gálvez, Guadalupe-Elide Morales-Figueroa , José-Antonio Arias-Montaño. The Histamine H3 Receptor: Structure, Pharmacology, and Function ,J. Molecular Pharmacology, (2016); 90(5):649-673
23. M S Airaksinen, P Panula,The histaminergic system in the guinea pig central nervous system: an immunocytochemical mapping study using an antiserum against histamine.J.J Comp Neurol. (1988) ;273(2):163-86
24. A E Alewijnse, H Timmerman, E H Jacobs, M J Smit, E Roovers, S Cotecchia, R Leurs, The effect of mutations in the DRY motif on the constitutive activity and structural instability of the histamine H(2) receptor,J.Mol Pharmacol. (2000);57(5):890-8
25. Florence Gbahou, Ludwig Vincent, Marie Humbert-Claude, Joel Tardivel-Lacombe, Claude Chabret, Jean-Michel Arrang,Compared pharmacology of human histamine H3 and H4 receptors: structure–activity relationships of histamine derivatives,J.Br J Pharmacol. (2006); 147(7):744-54.
26. EkateriniTiligada, 1 Konstantinos Kyriakidis, 1 Paul L. Chazot, 2 and M. Beatrice Passani,Histamine Pharmacology and New CNS Drug TargetsCNS NeurosciTher. (2011); 17(6):620–628.
27. Elden Berla Thangam,1 Ebenezer Angel Jemima, Himadri Singh, Mirza Saqib Baig, Mahejibin Khan, Clinton B. Mathias,5 Martin K. Church,The role of histamine and histamine recepters in mast cell and mediated allergy,J.Front Immunol. (2018); 9:1873
28. Dr. Sruthi M., MBBS,How do histamine antagonist-inverse agonists work? Medical BHMS, PGD Health Operations,J.Front SystNeurosci.(2012); 6(72):145-256
29. Jean-Charles Schwartz,The histamine H3 receptor: from discovery to clinical trials with pitolisant".J.Br J Pharmacol (2011);163(4):713-21.
30. Michael Berlin, Christopher W. Boyce, and Manuel de Lera Ruiz,Histamine H3 Receptor as a Drug Discovery Target".J. of Medicinal Chemistry.(2011); 54 (1):26–53
31. pillot c, ortiz j, héron a, ridray s, schwartzjc, arrangjm J.neuroscienceciproxifan, a histamine h3-receptor antagonist/inverse agonist, potentiates neurochemical and behavioral effects of haloperidol in the rat (2002)22 (16);7272–80
32. X. Ligneau, j.-s. Lin, g. Vanni-mercier, m. Jouvet, j. L. Muir, c. R. Ganellin, h. Stark, s. Elz, w. Schunack and j.-c. Schwartz neurochemical and behavioral effects of ciproxifan, a potent histamine h3-receptor antagonist journal of pharmacology and experimental therapeutics november(1998); 287(2):658-666;
33. Witkin jm, nelson dlselective histamine h3 receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous systemnists for treatment of cognitive deficiencies and other disorders of the central nervous system".J. Pharmacology ther. 103 (1): 1–doi:10.1016/j.pharmthera. (2004).05.001. Pmid 15251226; 1-20.
34. Charles h. Pierce "effects of using betahistine to treat adults withattention deficit hyperactivity disorder" J.clinical trial number nct00829881(2009); 108-259
35. Adrion, c; fischer, c. S.; wagner, j; "efficacy and safety of betahistine treatment in patients with meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial. J. clinical trial bmj. (2016); 21:10-1136
36. Yahiya y syed,pitolisant: first global approval drugs. J. 76 (13)doi:10.1007/s40265-016-0620-1. Pmid 27438291. S2cid 4268483 (2016); 1313-1318
37. "Pitolisant Orphan Drug Designations and Approvals". U.S. Food and Drug Administration.(FDA). 17 May 2010. Retrieved (2021); 47(16):111-215
38. Haibindai ,qiuli fu, yaoshen, weiwei hu, zhongmiaozhang, henktimmerman, rob leurs, zhongchen ,the histamine h3 receptor antagonist clobenpropit enhances gaba release to protect against nmda-induced excitotoxicity through the camp/protein kinase a pathway in cultured cortical neurons European.J.pharmacol. (2007); 1:117-23.
39. Sahlholm K, Nilsson J, Marcellino D, Fuxe K, Arhem P.; The human histamine h3 receptor couples to girk channels in xenopus oocytes; . European journal of pharmacology, (2007); 206-210
40. Anirban ghoshal ,ajeetkumar , doddapaneniyugandhar , chandansona , sunukuriakose , identification of novel β-lactams and pyrrolidinone derivatives as selective histamine-3 receptor (h3r) modulators as possible anti-obesity agents, eur.J.med chem. (2018); 25 152:148-159
41. Chungping Yu, Jennie GO, Shawn C, Stefan S, Vladimir M. New Insights into the Mechanism of Actionof Viloxazine: Serotonin and Norepinephrine Modulating Properties. Journal of experimental Pharmacology. (2020); 25:285-300.
42. Findling RL, Candler SA, Nasser AF, Schwabe S, Yu C, Garcia J, O'Neal W, Newcorn JH. Viloxazine A New Non-Stimulant Option in the Treatment of Pediatric Attention-Deficit/Hyperactivity Disorder. Journal of Psychosocial Nursing and Mental Health Services. (2022); (4) 7-9.
43. Elisabetta Baldi,CorradoBucherelli, Walter Schunack, Gabriele Cenni, Patrizio Blandina, M Beatrice Passani,The H3 receptor protean agonist proxyfan enhances the expression of fear memory in the rat,J.Neuropharmacology(2005); (2):246-51.
44. F.P. Jansen, Characterization of the binding of the first selective radiolabelled histamine H3-receptor antagonist, 125I-iodophenpropit, to rat brain T.S. Wu, H.-P. Voss, H.W.M. Steinbusch, R.C. Vollinga, B. Rademaker, A. Bast, H. Timmerman,J. British Journal of Pharmacology.(1994); 113(2):355–62
45. Krueger, KM; Witte, DG; Ireland-Denny, L; Miller, TR; Baranowski, JL; Buckner, S; Milicic, I;Esbenshade, TA; Hancock, AA, "G protein-dependent pharmacology of histamine H3receptor ligands: evidence for heterogeneous active state receptor conformations".Journal of Pharmacology and Experimental Therapeutics.(2005); 314 (1):271–81
46. X Ligneau 1, M Garbarg, M L Vizuete, J Diaz, K Purand, H Stark, W Schunack, J C Schwartz,Iodoproxyfan, a new antagonist to label and visualize histamine H3 receptors. J Pharmacology Experiment Theory ,(1994); 271(1):452-9
47. Pillot C, Heron A, Cochois V, Tardivel-Lacombe J, Ligneau X, Schwartz JC, Arrang JM. A detailed mapping of the histamine H(3) receptor and its gene transcripts in rat brain. Thioperamide". IUPHAR/BPS Guide to Pharmacology .J.Neuroscience, (2002); 114 (1):173-93.