International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

EMERGING TRENDS IN DRUG TARGETING OF COMPLEX NEUROLOGICAL DISORDERS: A REVIEW ON H_3 RECEPTOR ANTAGONISTS: A RREVIEW

Bhawna Khurana[*1], Lohit Girotra[1], Ritesh Bajaj[1], Dr. M.M Gupta[1]

[1]Jaipur College of Pharmacy, affiliated to Rajasthan University of Health Sciences, Jaipur, India.

ABSTRACT

The discovery of the third histamine receptor that is H3-receptor and its highly potent and selective ligands has illuminated various aspects of histaminergic neurotransmission in the brain. This biogenic amine is found to be present presynapticaly in different areas of the mammalian brain (widely distributed in the cortex of the brain). It is not only involved in regulation of histamine but also variety of other neurotransmitters such as norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine and gammaaminobutyric acid. Current neurological studies have demonstrated a leeway of the clinical efficacy of selective H3-receptor antagonists in various CNS disorders including cognitive/ vigilance deficits, sleep disorders, epilepsy, obesity, Alzheimer's disease (AD), schizophrenia, attention deficit hyperactive disease (ADHD), Parkinson's disease, stress, anxiety, etc. This review focuses on the role of H3-receptor in neurological effects as well as provides an update on selective H3-receptor antagonists in various states of preclinical and clinical advancement.

KEYWORDS : *H3-receptor, histamine, H3-receptor antagonists, CNS disorders*

Correspondence Author

Bhawna Khurana

Jaipur College of Pharmacy, affiliated to Rajasthan University of Health Sciences, Jaipur, India.

Email: bhavna.khurana89@gmail.com

INTRODUCTION

Histamine is a naturally occurring imidazole derivative, widely distributed in skin, GIT mucosa, lungs, brain, CSF and bone marrow. It can be released from the mast cells by a choice of mechanisms such as Immunological Release, Chemical and Mechanical release, Drug release[1-3].

There are four histamine receptors that have been acknowledged: H1, H2, H3, and H4[4-7].In common, H1-receptor has revealed to alter inflammatory responses such as allergic reactions and H2-receptor to alter gastric acid secretion. This led to the sighting and therapeutic use of persuasive H1 and H2-receptor antagonists. In disparity to H1, H2, and H4-receptors, H3-receptor are chiefly expressed in the CNS[6-7], act as autoreceptors in presynaptic neurons, and control histamine turnover. H3-receptor has shown to possess the activity of heteroreceptors in case of dopamine-, serotonin-, noradrenaline- , GABA-, and acetylcholine-containing neurons[8]. H3-receptor act by transforming brain histaminergic tone as they

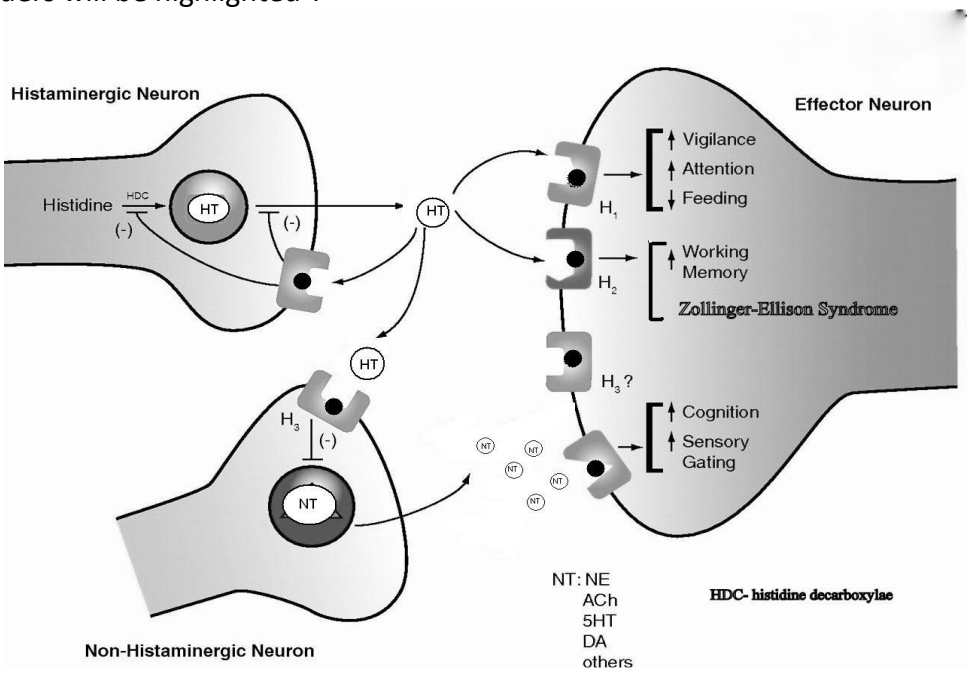
are highly concentrated in CNS and possibly by interacting with H1 and H2-receptors. Histamine has been concerned with the regulation of arousal state[9], locomotor activity[10], cardiovascular control[11], water intake[12], food intake[13], and memory formation[14]. The functions of H3-receptor with respect to the pharmacological effects of histamine in the CNS are not so clear.

From the above mentioned facts, it is very clear that histamine is responsible for the repression of appetite as it inhibits the gastric acid secretion and its depletion stimulate feeding[15].

The aim of this paper is to review some of the important recent advances in understanding the molecular and functional aspects of the H3-receptor with respect to the role of this receptor in neurological disorders. In addition, the preclinical properties of some H3-receptor antagonists that have recently advanced into human clinical studies for cognitive disorders will be highlighted[2].

MODE OF ACTION OF HE- RECEPTOR

Stimulation of presynaptic H_3 autoreceptors on histaminergic neurons by histamine (HA) inhibits the synthesis of histamine [through histidine decarboxylase (HDC)] and also inhibits the release of HA from the neuron. Likewise, stimulation of presynaptic H_3 heteroreceptors on non-histaminergic neurons inhibits the release of a number of neurotransmitters (NT), including norepinephrine (NE), acetylcholine (ACh), serotonin (5HT), dopamine (DA), and others. These neurotransmitters can then activate their respective target receptors postsynaptically to stir up a variety of physiological responses as indicated in the figure[16].



PRE-CLINICAL ISSUES WITH THE DEVELOPMENT OF H3R ANTAGONISTS

The H3-receptor involves a basic amine linked to an aromatic/lipophilic region that is connected to either:

1. A second basic site;
2. A polar group or
3. A lipophilic region[19, 37-38],

Which makes the H3R antagonists prone to hERG inhibition and phospholipidosis[38] (Altenbach, personal communication).

Therefore, every H3-receptor antagonist programme should take these parameters into consideration as early as possible Furthermore; all tested Evotec compounds illustrated no sign of phospholipidosis. These facets are hardly desirable

in a molecule that is aiming to treat chronic illnesses. As discussed below, one of the challenges with H3-receptor antagonist design is overcoming the similarity between the H3-receptor[27, 37-38] and hERG pharmacophores.

Chronologically defined H-3 Receptor antagonists contemplate the following pre-clinical issues regarding their pharmacological role:

1. **Imidazole-containing compounds**, such as Gliatech's clinical candidate GT-2331[16], were possibly terminated because of the intrinsic risk related with the silencing of cytochrome P450 isoenzymes, resulting in undesirable drug– drug interactions[17-18].
2. **Non-imidazole classes** of H3-receptor antagonists appear not to inhibit radically the CYP family of enzymes, many H3-receptor antagonists face blockade of the hERG K+ channel[21-23] or have established the potential for phospholipidosis[21, 24] or they have dealt with P-gp substrate problems.

   As an example, Abbott's pre-clinical candidate ABT-239 is reported to exhibit strong binding to the hERG K+ channel that manifested itself in a dose-dependent QTc prolongation in dog (Altenbach, personal communication) and monkey[25].
3. **Molecular modeling of the H_3R** has been used to diminish the low nanomolar strength of dibasic H3-receptor antagonists such as JNJ-5207852. The two basic piperidine sites can simultaneously form strong piperidine saltbridge interactions to Asp-114 on helix III and Glu-206 on helix V, which are believed to be the key dregs that histamine interacts with to alleviate the active state of the receptor.

   Further, Abbott's recent published patent applications, US2007066588A1 and WO2007150010A2 have concentrated on replacement of the 2-ethylaminobenzofuran core present in ABT-239. This modification has been reported to reduce the hERG liability[26].
4. **Dibasic H3-receptor antagonists** exhibit sub-nanomolar potency[28-29] and disease relevant in vivo models[30-32], dibasic H3-receptor antagonists can have long brain residence times in rat[33-34].

H3- RECEPTORS IN NEUROLOGICAL ASPECTS

Histamine H3-receptor antagonist [3H]GSK189254 have been used to investigate H3-receptor binding in the amyloid over-expressing double mutant APPswe × PSI.MI46V (TASTPM) transgenic mouse model of AD and in post-mortem human AD brain samples for their potential use in Alzheimer's disease (AD)[39-40]. Similarly BF2.649 showed significant inhibitory activity in several mouse models of schizophrenia. It reduced locomotor hyperactivity elicited by methamphetamine or dizolcipine without significantly affecting spontaneous locomotor activity when administered alone[41-42]. Extra pyramidal effects like in Parkinson's disease (PD), there is an increase in histamine levels and in the varicosity size and density of histamine fibers in the substantia nigra. Furthermore, H3-receptor binding density is elevated in the SN in Parkinson's disease. H3 binding sites are particularly abundant in the substantia nigra, but there is only low expression of the mRNA for H3-receptors. 5-hyroxy tyramine (5-HT) is released from SN which is responsible for Parkinson's disease. It was seen that there is a potent inhibition of 5-HT on administration of H3-receptor antagonists[52].

Beside these diseases histamine H3-receptors are involved in arousal disorders (e.g.

Attention deficit hyperactivity disorder - ADHD) which imparts cognitive impairment involving a complex mental process which integrates awareness, perception, reasoning, language, memory and judgment[43-44]. The identification of H3-receptor antagonists has received considerable attention in the field of attention and cognitive disorders since first generation antagonists were shown to promote attention and wakefulness and improve short-term and social memory in rodents. A-304121, A-317920 and A-349821 have demonstrated efficacy in animal models and a new molecule, ABT-239 has high affinity and selectivity for human H3-receptors, good oral bioavailability and excellent blood brain barrier penetration. It is a

potent stimulator of memory so can be used to treat broad range of cognitive disorders.

The ability of H3 antagonists like Ciproxifan as amyloid precursor protein (APP) to enhance memory in normal animals and in pharmacological models of memory impairment raises the possibility that such compounds may represent an effective treatment strategy for Alzheimer's disease[47]. Also DOPAC/dopamine ratios were enhanced in the prefrontal cortex but not in the striatum, indicating a selective activation of a sub-population of dopaminergic neurons in case of schizophrenia. It also abolished the apomorphine-induced deficit in prepulse inhibition[44-45].

The role of Histamine H3-receptors is also of significance in promoting wakefulness and has been shown to be deficient in hypocretin-deficient animal models for narcolepsy. Orexin/hypocretin abnormalities in narcolepsy have been linked to abnormalities of the histaminergic system[46]. However, Kanbayashi and colleagues have observed that CSF histamine concentrations are low in both hypocretin-deficient and nondeficient human narcoleptics when compared with neurologic controls. This comprehended that Histamine H3-receptor are inhibitory autoreceptors and H3 antagonists may promote wakefulness with fewer adverse effects[50]. Shiba and colleagues used a mouse narcolepsy model to assess the wake-promoting effects of thioperamide, a potent H3 antagonist. Thioperamide increased wakefulness and reduced NREM and REM sleep in a dose-dependent manner in both hypocretin/orexin-deficient (narcoleptic) and wild-type mice[51]. The hypocretin/orexin-deficient mice were more sensitive to the wake-promoting effects of thioperamide[48-49] .

Table summarizes the relation of H3-receptor in neurological disorders[39-50]:-

Neurological Disorder	Cause	H3 Receptor Antagonists	Mode of Action
1. Alzheimer's Disease	amyloid plaques & tangled bundles of fibers	[3H]GSK189254	binding was detected in sections of human medial frontal cortex from AD brains of varying disease severity
2. Schizophrenia	abnormal increase in dopamine activity in the striatum	BF2.649	DOPAC/dopamine ratios were enhanced in the prefrontal cortex indicating a selective activation of a sub-population of dopaminergic neurons.
		Zyprexa	Inverse the action of dopamine and seratonin
3. Parkinson's disease	decreased dopamine activity in the basal ganglia	clobenpropit and thioperamide	Increases the dopamine level by GABA mechanism
4. Attention deficit	Combination of various	ABT-239	Not Known

hyperactive disease	genes, many of which affect dopamine transporters but specific cause is still unknown.	PF-03654746	? Novel Mechanism of Action (in a decongestant study)
5. Narcolepsy	an abnormality in the orexin (hypocretin) system (hypothalamic neuropeptides)	Thioperamide	Increases wakefulness by increasing the histamine level

DOPAC- dihydroxyphenylalanine, AD- Alzheimer's disease, BF2.649 - 1-{3-[3-(4-chlorophenyl) propoxy]propyl} piperidine

FUTURE ASPECTS OF H-3 RECEPTOR ANTAGONISTS[3]

- In CNS & ANS, the presynaptic H3-receptor serves as feedback inhibitors to histamine and NE release. Search for selective agonists at H3-Receptor may provide a drug which may prevent cardiac arrhythmias and cardiac damage that may result from NE discharge during ischaemia or stress.
- Activation of H3-receptor by such agonists would also inhibit gastric acid release and would block certain inflammatory processes. Such drug can open a plethora of newer antiulcer drugs which may be safer than H2-receptor antagonists.
- Another pre-requisite for successful drug development is that a compound should influence different neurotransmitter systems in a temporally controlled manner. For example, pain-reducing agents should be active over a 24-hour period but, ideally, should not affect nocturnal sleep. Given the alerting manners of H3-receptor antagonists this would seem to pose a significant challenge. The published study with BF2.649 is hopeful in this respect as it shows that it might be possible to reduce daytime sleep episodes without affecting nocturnal sleep significantly.

CONCLUSION

From the above facts we can conclude that H3-receptors are the receptors of immense importance in case of neurological disorders. There is a complex biology associated with these receptors due to its heterogeneity in molecular, pharmacological & functional properties. The maintenance of H3-receptor integrity in different disorders like Alzheimer's disease, Parkinson's disease, epilepsy etc for a novel therapeutic approach for the symptomatic treatment of same is of great importance. Much of the interest in the therapeutic potential of H_3 antagonists arises from the ability of H_3 antagonists to enhance the release of key neurotransmitters such as histamine, ACh, norepinephrine and dopamine that play critical roles in cognitive processing. Despite these many advances, to date no clinical proof of concept for an H3-receptor antagonist has been reported. However, a number of clinical studies examining the efficacy of H3-receptor antagonists for a variety of cognitive disorders are currently underway. In the near future, research efforts are sure to continue to gain further insights into the functions of the H3-receptor in the quest to discover selective therapeutic H_3 antagonists for the novel treatment of cognitive disorders.

REFERENCES

1. Divya Vohora, S.N. Pal, K.K. Pillai. Histaminergic H3 -Receptors as Modulators of CNS Function.

Indian Journal of Pharmacology 2001; 33: 17-28.
2. T A Esbenshade, K E Browman, R S Bitner, *et al*. The histamine H_3 receptor: an attractive target for the treatment of cognitive disorders. Abbott Laboratories, Abbott Park, IL, USA:2008.
3. Sharma & Sharma chapter26 paras publications, 1sr edition 2007 pg no. 340- 34.
4. Schwartz, J.C., and Haas, H.L. 1992. *The histamine receptor.* Wiley Liss. New York, New York, USA
5. Leurs R, Smit MJ, Timmerman H. Molecular pharmacological aspects of histamine receptors. *Pharmacol. Ther.* 1995; 66:413–463.
6. Lovenberg TW, *et al*. Cloning and functional expression of the human histamine H3 receptor. *Mol. Pharmacol.* 1999;55:1101–1107.
7. Oda T, Morikawa N, Saito Y, *et al*. Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. *J. Biol. Chem.* 2000;275:36781–36786.
8. Schlicker E, Malinowska B, Kathmann M, *et al*. Modulation of neurotransmitter release via histamine H3 heteroreceptors. *Fundam. Clin.Pharmacol.* 1994;8:128–137.
9. Lin JS, *et al*. Involvement of histaminergic neurons in arousal mechanisms demonstrated with H3-receptor ligands in the cat. *Brain Res.* 1990;523:325–330.
10. Clapham J, Kilpatrick GJ. Thioperamide, the selective histamine H3 receptor antagonist, attenuates stimulant-induced locomotor activity in the mouse. *Eur. J. Phamacol.* 1994;259:107–114.
11. Imamura M, Smith NC, Garbarg M, *et al*. Histamine H3-receptor-mediated inhibition of calcitonin gene-related peptide release from cardiac C fibers. A regulatory negative-feedback loop. *Circ. Res.* 1996;78:863–869.
12. Lecklin A, Etu-Seppala P, Stark H, *et al*. Effects of intracerebroventricularly infused histamine and selective H1, H2, and H3 agonists on food and water intake and urine flow in Wistar rats. *Brain Res.* 1998;793:279–288.
13. Leurs R, Blandina P, Tedford C, *et al*. Therapeutic potential of histamine H3 receptor agonists and antagonists. *Trends Pharmacol. Sci.* 1998;19:177–184.
14. Blandina P, *et al*. Inhibition of cortical acetylcholine release and cognitive performance by histamine H3 receptor activation in rats. *Br. J. Pharmacol.* 1996;119:1656–1664.
15. Tuomisto L, Yamatodani A, Jokkonen J, Sainio EL, Airaksinen MM. Inhibition of brain histamine synthesis increases food intake and attenuates vasopressin response to salt loading in rats. *Meth. Find. Exp. Clin. Pharmacol.* 1994;16:355–359.
16. Timothy A, Esbenshade,Gerard B, Fox &Marlon D, *et al*. "Histamine H_3 Receptor Antagonists: Preclinical Promise for Treating Obesity and Cognitive Disorders". American Society for Pharmacology and Experimental Theraputics 2006.
17. Boxenbaum, H. (1999) Cytochrome P450 3A4 in vivo ketoconazole competitive inhibition: determination of Ki and dangers associated with high clearance drugs in general. J. Pharm. Pharm. Sci. 2, 47–52.
18. Lin, J.H. and Lu, A.Y.H. (1998) Inhibition and induction of cytochrome P450 and the clinical implications. Clin. Pharmacokinet. 35, 361–390.
19. Wijtmans, M. *et al*. (2007) Histamine H-3 receptor ligands break ground in a remarkable plethora of therapeutic areas. Expert Opin. Invest. Drugs 16, 967–985.
20. Cowart, M. *et al*. (2004) Medicinal chemistry and biological properties of nonimidazole histamine H-3 antagonists. Mini Rev. Med. Chem. 4, 979–992.
21. Sun, M.H. *et al*. (2005) Synthesis and SAR of 5-amino- and 5- (aminomethyl)benzofuran histamine H-3 receptor antagonists with improved potency. J. Med. Chem. 48, 6482–6490.
22. Nagase, T. *et al*. (2008) Synthesis, structure–activity relationships, and biological profiles of a quinazolinone class of histamine H-3 receptor inverse agonists. J. Med. Chem. 51, 4780–4789.

23. Lau, J.F. *et al*. (2006) Ureas with histamine H-3-antagonist receptor activity – a new scaffold discovered by lead-hopping from cinnamic acid amides. Bioorg. Med. Chem. Lett. 16, 5303–5308.
24. Zhao, C. *et al.*(2008) The alkaloid conessine and analogues as potent histamine H-3 receptor antagonists. J. Med. Chem. 51, 5423–5430.
25. Hancock, A.A. (2006) The challenge of drug discovery of a GPCR target: analysis of preclinical pharmacology of histamine H-3 antagonists/inverse agonists. Biochem. Pharmacol. 71, 1103–1113.
26. Altenbach, R.J. *et al*. (2007) Synthesis, potency, and in vivo profiles of quinoline containing histamine H-3 receptor inverse agonists. J. Med. Chem. 50, 5439–5448.
27. Axe, F.U. *et al*. (2006) Three-dimensional models of histamine H-3 receptor antagonist complexes and their pharmacophore. J. Mol. Graph. Model. 24, 456–464.
28. Esbenshade, T.A. *et al*. (2004) Pharmacological and behavioral properties of A- 349821, a selective and potent human histamine H-3 receptor antagonist. Biochem. Pharmacol. 68, 933–945.
29. Fox, G.B. *et al*. (2002) Differential in vivo effects of H-3 receptor ligands in a new mouse dipsogenia model. Pharmacol. Biochem. Behav. 72, 741–750.
30. Esbenshade, T.A. *et al*. (2006) Histamine H-3 receptor antagonists: preclinical promise for treating obesity and cognitive disorders. Mol. Interv. 6, 77–88.
31. *et al*Fox, G.B. *et al.*(2003) Two novel and selective nonimidazole H-3 receptor antagonists A-304121 and A-317920: II. In vivo behavioral and neurophysiological characterization. J. Pharmacol. Exp. Ther. 305, 3897–3908.
32. Barbier, A.J. *et al*. (2004) Acute wake-promoting actions of JNJ-5207852, a novel, diamine-based H-3 antagonist. Br. J. Pharmacol. 143, 649–661.
33. Bonaventure, P. *et al*. (2007) Histamine H-3 receptor antagonists: from target identification to drug leads. Biochem. Pharmacol. 73, 1084–1096.
34. Santora, V.J. *et al*. (2008) Novel H-3 receptor antagonists with improved pharmacokinetic profiles. Bioorg. Med. Chem. Lett. 18, 4133–4136.
35. Santora, V.J. *et al*. (2008) A new family of H-3 receptor antagonists based on the natural product Conessine. Bioorg. Med. Chem. Lett. 18, 1490–1494.
36. Apodaca, R. *et al*. (2003) A new class of diamine-based human histamine H-3 receptor antagonists: 4-(aminoalkoxy)benzylamines. J. Med. Chem. 46, 3938–3944.
37. Roche, O. and Sarmiento, R.M.R. (2007) A new class of histamine H-3 receptor antagonists derived from ligand based design. Bioorg. Med. Chem. Lett. 17, 3670– 3675.
38. Lazewska, D. *et a*l. (2008) Piperidine variations in search for non-imidazole histamine H3 receptor ligands. Bioorg. Med. Chem. 16, 8729–8736.
39. *www.alz.org*
40. Ligneau, X. *et al*. J Pharmacol Exp Ther 1998: 287,658-666.
41. Moyer, Paula . "CAFE Study Shows Varying Benefits Among Atypical Antipsychotics". Medscape Medical News (WebMD). Retrieved 2007-12-03. de Haan L, van Amelsvoort T, Rosien K, Linszen D (2004). "Weight loss after switching from conventional olanzapine tablets to orally disintegrating olanzapine tablets". Psychopharmacology (Berl) 175 (3): 389–90. doi:10.1007/s00213-004-1951-2. PMID 15322727.
42. Xavier Ligneau, *et al*, Régis Parmentier, *et al* and Aude Burban, *et al*. Brain histamine and schizophrenia: potential therapeutic applications of H3-receptor inverse agonists studied with BF2.649. Biochemical Pharmacology / Biochemistry and Pharmacology:2007:73:1215-24.
43. Volkow, ND; Wang, GJ; Kollins, *et al*. (2009). "Evaluating Dopamine Reward Pathway in ADHD". *JAMA* **302** (10): 1084–1091.

44. Lead discovery Report on Abbott's H3 histamine receptor antagonist, ABT-239, a candidate treatment of cognitive disorders, ADHD, Alzheimer's and schizophrenia.
45. Patrik Munzar, Gianluigi Tanda, Zuzana Justinova, *et al*. Histamine H3 Receptor Antagonists Potentiate Methamphetamine Self-Administration and Methamphetamine-Induced Accumbal Dopamine Release**.** Received 23 July 2003; Revised 4 December 2003; Accepted 7 December 2003; Published online 21 January 2004.
46. Shiba T, Fujiki N, Wisor JP, *et al*. Wake promoting effects of thioperamide, a histamine H3 antagonist in orexin/ataxin-3 narcoleptic mice. Program and abstracts of the Associated Professional Sleep Societies 18th Annual Meeting; June 5-10, 2004; Philadelphia, Pennsylvania. Abstract 542.
47. Medhurst, AD; Roberts, JC; Lee, J; *et al*. Characterization of histamine H_3 receptors in Alzheimer's Disease brain and amyloid over-expressing TASTPM mice. British Journal of Pharmacology, Volume 157, Number 1, May 2009 , pp. 130-138(9).
48. Lin L, Faraco J, Li R, *et al*. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell. 1999;98:365-376.
49. Nishino S, Fujiki N, Ripley B, *et al*. Decreased brain histamine content in hypocretin/orexin receptor-2 mutated narcoleptic dogs. Neurosci Lett. 2001;313:125-128.
50. Kanbayashi T, Kodama T, Kondo H, *et al*. CSF histamine and noradrenaline contents in narcolepsy and other sleep disorders. Program and abstracts of the Associated Professional Sleep Societies 18th Annual Meeting; June 5-10, 2004; Philadelphia, Pennsylvania. Abstract 529.
51. Shiba T, Fujiki N, Wisor JP, *et al*. Wake promoting effects of thioperamide, a histamine H3 antagonist in orexin/ataxin-3 narcoleptic mice. Program and abstracts of the Associated Professional Sleep Societies 18th Annual Meeting; June 5-10, 2004; Philadelphia, Pennsylvania. Abstract 542.
52. Sarah Threlfell, Stephanie J. Cragg, Imre Kalló, *et al*. Greenfield. Histamine H_3 Receptors Inhibit Serotonin Release in Substantia Nigra Pars Reticulata.The Journal of Neuroscience, October 6, 2004, 24(40):8704-8710.

*****