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Histamine H_3 Receptor Function and Ligands: Recent Developments

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Abstract: Histamine H_3 receptors are found mostly in central nervous system involved in the regulation of release of various neurotransmitters in brain. They have been implicated in diverse potential therapeutic applications such as sleep-wake disorders, attention-deficient hyperactivity disorder, epilepsy, cognitive impairment and obesity. This review is an attempt to elucidate the function of H_3 receptors and their role in various CNS disorders. Also, it is aimed at collating the information on efforts of various medicinal chemists to synthesize the H_3 receptor agonists and antagonists in single article.

Keywords: Epilepsy, H_3 Receptors, Obesity, H_3 Receptor Antagonists.

INTRODUCTION

Histamine (HA) plays a key role in functioning of central and peripheral tissues. It is one of the important local chemical mediators and neurotransmitters found in human body [1]. In the central nervous system (CNS), histamine is stored in vesicles of histaminergic neurons, which are located only in tuberomammilary nucleus of hypothalamus [2]. It is produced by decarboxyalation of histidine and it has wide range of physiological and pathophysiological functions in body [3, 4]. Histamine receptor has four subtypes, out of which, antagonists of H_1 receptors (H_1R) and H_2 receptors (H_2R) are widely used for treatment of allergy and ulcer, respectively [5]. H_3 histamine receptors (H_3R) are found in CNS and to a lesser extent peripheral nervous system (PNS). These receptors, when occupied by histamine, cause decrease in release of neurotransmitters such as histamine, Gamma Amino Butyric Acid (GABA), Acetyl Choline (ACh), Norepinephrine (NE), Serotonin (5HT), and Dopamine (DA). H_4 histamine receptors are found primarily in the basophils, thymus, small intestine, spleen, colon, bone marrow and play a role in chemotaxis [6].

H_3 RECEPTOR AND ITS FUNCTION IN CNS

Arrang *et al.* in 1983 recognized H_3R and its role in Central Nervous System (CNS) as presynaptic auto receptor. Later, it was realized that H_3R is hetero as well as auto-receptor. Activation of H_3R reduces the release and deactivation increases the release of various neurotransmitters in brain (Fig. **1**) [7, 8]. Presynaptic neuronal control via H_3 receptors is an important regulatory mechanism of HA mediated neurotransmission [9]. Histaminergic neurons are exclusively found in tuberomammilary nucleus of posterior hypothalamus and control all major areas of brain which are involved in sleep, wakefulness, cognition, transmission and various CNS functions [10].

The cloning of human H_3R was done in 1999 by Lovenberg and co-workers [11]. The overall sequence homology of the H_3R to H_1R and H_2R is only 22% and 20%, respectively [12]. The gene of H_3R has complex structure, so a large number of H_3R isoforms exist. This is possible because of alternative splicing of H_3R mRNA. The H_3R gene consists of three exons and two introns. So far, at least 20 isoforms of the human H_3R have been identified on the basis of detection of varying mRNAs, but their regional expression and function remains largely unknown. The full-length H_3R (445 amino acids) is currently the best characterized isoform [13]. Most splice variants have deletions in the e3 loop, an important region involved in G protein coupling. In recombinant systems, it has been shown that these isoforms have altered signaling properties compared to the full-length receptor [14].

Stimulation of H_3R gives negative feedback about the synthesis of HA via adenylate cyclase (AC) inhibition. AC catalyzes the formation of the second messenger cyclic adenosine mono phosphate (cAMP) and reduction of cAMP levels leads to inhibition of histidine decarboxylase (HDC), a key enzyme in histamine synthesis. Thus, activation of H_3R leads to decrease in histamine synthesis in presynaptic histaminergic neurons (Fig. **2**) [15].

The released HA, via presynaptic H_3R decreases the further release of HA and also inhibits release of various other neurotransmitters such as GABA, DA, NE, 5HT etc. Thus, H_3R helps in inhibitory control of histaminergic neurons via HA, as well as of the postsynaptic histamine receptors.

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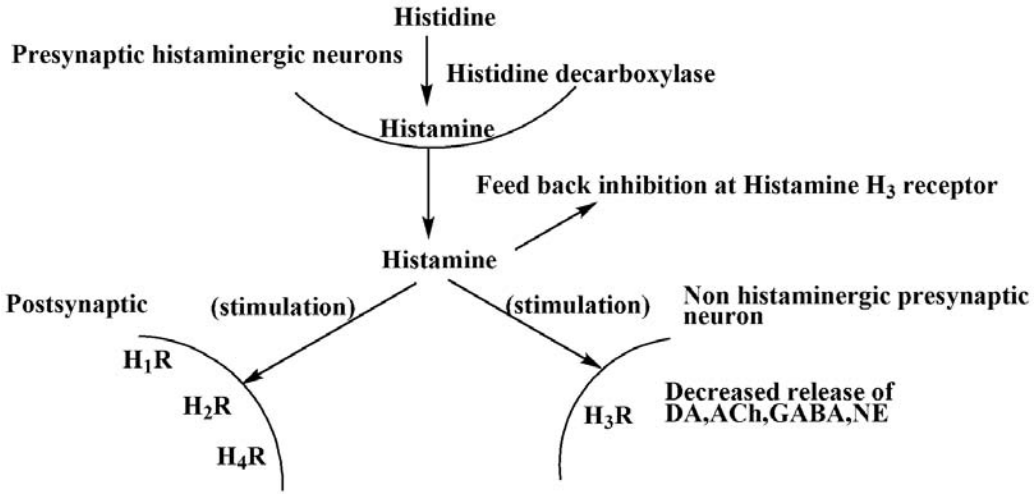

Fig. (1). H_3R Auto- and hetero- receptor function in central nervous system.

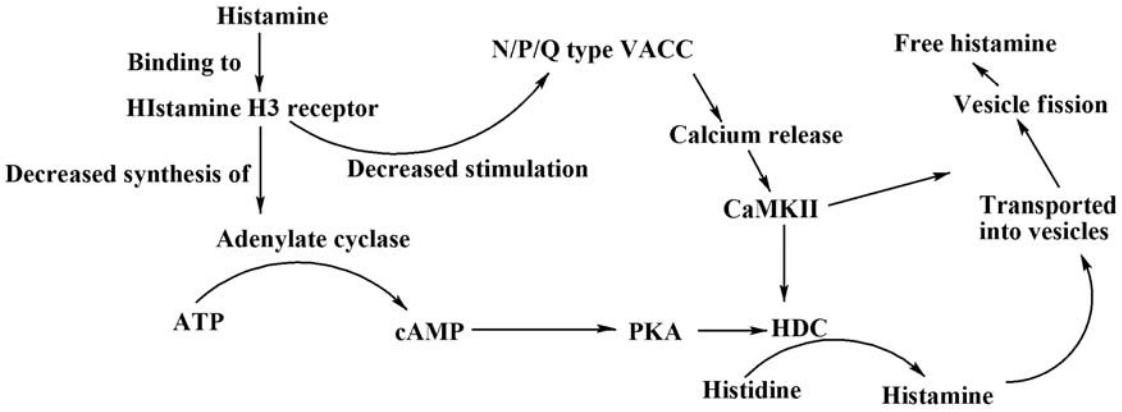

Fig. (2). H_3R-mediated signal transduction – histamine synthesis and release. H_3R, histamine H_3 receptors: AC, adenylate cyclase; PKA, protein kinase A; HDC, histidine decarboxylase; VACC, voltage-activated calcium channels; CaMKII, calmodulin kinase II.

H_3 RECEPTORS AND ROLE IN EPILEPSY

Almost 50 years ago first clinical indication suggesting the involvement of central HA mediated neurotransmission in epilepsy was reported [16, 17]. H_1 receptor activation or modulation of CNS HA levels by L-histidine loading and inhibition of metabolism of HA in rodents indicates that HA can be an endogenous antiepileptic [18]. The role of H_1 receptors in epilepsy was further supported by an increased H_1 receptor density (10 to 50 %) by focusing on epileptic discharges in the temporal neo cortex of patients with complex partial seizures and also by observation that in several young children, H_1 receptor antagonists often produced convulsions [19, 20].

The involvement of HA in epileptic seizures has long been recognized based on the proconvulsant properties of histamine antagonists [21]. Histamine receptor ligands, which increase histamine levels, such as histidine and histamine N-methyl transferase (HNMT) inhibitors (eg. metoprine) reduce seizures in epileptic patients via H_1 mediated excitation [22-24]. H_3R antagonists such as thioperamide, clobenpropit, AQ0145 also decrease the seizure susceptibility of electrically induced convulsions in mice [25]. These compounds act by increasing endogenously released HA in the brain [26, 27]. The anticonvulsant effect of these compounds can be antagonized by giving H_3R agonists (immepip) or H_1 receptor antagonist (mepyramine). These research findings suggest that H_3R antagonists could represent a new way in the development of antiepileptic drugs.

H_3R modulates release of various neurotransmitters such as NE, ACh, DA, 5HT and GABA. H_3R activation reduces release of NE in rat hypothalamus. Experiments have shown that H_3R activation decreases the release of ACh in rat cortex. In mouse stratial tissue, DA release is also reduced by histamine receptor activation. DA induced release of GABA is also inhibited by H_3R activation and presynaptic H_3R mediated release of glutamate has been reported.

H_3R and GABA Release

The H_3R antagonist clobenpropit enhances release of GABA from rat hypothalamus [28, 29]. GABA is an inhibitory neurotransmitter, which balances the excitatory activity in synapses in CNS. GABA, as neurotransmitter, slows electrical transmission between the nerve cells and helps in balancing

of nerve impulse. Low levels of GABA in the body have been linked to epilepsy and an increased risk for seizure. A number of the drugs used to treat epilepsy stimulate production of GABA [30].

H_3R and ACh Release

The relation of ACh with seizure has not been well established. ACh injection to the epileptic patient reduces the frequency of seizure. However, role of ACh in the treatment of epilepsy has been reported with different results [31]. ACh release was reduced by H_3R agonists like Imetit, alpha methyl histamine, etc. This reduced release of ACh was again enhanced by H_3R antagonists such as thioperamide. H_3R mediated ACh release from rat basolateral amygdale and hippocampal region has also been reported [32]. Histamine receptor agonist alpha methyl histamine and imepip directly administered to rat basolateral amygdale triggered spontaneous release of ACh and administration of H_3R antagonists eg. thioperamide, ciproxifan increased the release of acetylcholine via H_3R mediated neurotransmission [33, 34]. In the medial septum–diagonal band of freely moving rats, H_3R antagonists thioperamide and ciproxifan increased the release of hippocampal ACh, whereas R-α-methyl histamine, an H_3R agonist, produced the opposite effect [35]. So these findings suggest that H_3R antagonists have a profound effect on release of ACh and could be useful for treatment for epilepsy.

H_3R and 5HT Release

The substantia nigra pars reticulata (SNr) plays an important role in basal ganglia function. Substantia nigra pars reticulata is characterized by rich aminergic input that includes dopaminergic dendrites and axons containing 5HT or HA. The role of HA in the SNr is motor control via histamine H_3 receptors, the mechanism remains far from elucidated. Selective H_3R agonists R-α-methyl-histamine or immepip can inhibit the 5-HT release by up to 60% [36]. This inhibition can be prevented by the H_3R antagonists like thioperamide [37]. So H_3R antagonists can increase the serotonin release and gives a hope for treatment of epilepsy.

ROLE OF H_3R IN OTHER DISORDERS

Obesity

Hypothalamic histaminergic neurons interfere with orexigenic pathways and feeding behavior. Therefore, studies suggest that H_3R antagonists can be used for the treatment of obesity [38]. Elevated levels of central histamine reduce food intake and body weight in rodents [39]. HA activates postsynaptic H_1 receptors in the ventro medial nuclei of the hypothalamus to suppress appetite and HA containing neurons in the hypothalamus participate in the endogenous suppression of food intake. In addition, there are evidences that H_3R have been found in ventro medial nuclei region [40]. Feeding is suppressed in rat by Intra-cerebroventricular injections of HA, whereas the use of H_3R antagonists such as thioperamide also supressed feeding and depletion of endogenous HA exerts feeding response [41-44]. Dysfunctions in HA mediated neurotransmission have also been identified in obese zucker rats [45].

Sleep and Wakefulness

The histaminergic system performs a major role in the maintenance of sleep and wakefulness. The presence of HA containing cells in the tuberomammillary nucleus of the posterior hypothalamus has been identified. This area is mainly involved in the regulation of wakefulness and projections of these histaminergic neurons to the cerebral cortex suggest a role of HA in the modulation of the arousal state and sleep-wake cycle. Lesions of posterior hypothalamus produce sleep in rats, cats and monkeys [46]. The histaminergic neurotransmission promotes waking and alertness. Wake promoting activity of H_3R inverse agonists has been observed in cats, mice, rats, and guinea pigs [47-49]. Modulation of histamine levels mediated by H_3R agonists results in an increase of the slow-wave sleep in rats [50, 51]. Neurochemical and electrophysiological studies indicate that the activity of histaminergic neurons is maximal during periods of wakefulness and is depressed by barbiturates and other hypnotics [52, 53]. Moreover, in some *in vivo* studies, release of histamine in the rat hypothalamus shows a circadian rhythm, with higher histamine release in periods with high locomotors activity. On the contrary, systemic application of H_3R antagonists produce increased wakefulness (decreases in rapid eye movement (REM) and slow-wave sleep) and increased locomotion.

Cognition and Memory Processes

Dysfunction of ACh -mediated neurotransmission is one of the factors responsible for cognitive decline associated with ageing and Alzheimer's disease. Histaminergic modulation of hippocampal ACh release has been reported [54]. However, changes typical of ageing and Alzheimer's disease with alterations of other neurotransmitter systems, including HA have also been reported [55, 56]. There is direct evidence that histaminergic neurotransmission plays an important role in learning and memory.

In one of the studies, it was found that HA content was significantly reduced in the hypothalamus, hippocampus and temporal cortex of Alzheimer's brains. HA levels in other cortical areas, putamen and substantia nigra were not much different. Further, administration of HA enhanced cognitive performance of rats in an active avoidance task, while H_1R antagonists impaired memory retention [57]. Neurochemical studies also show that HA modulates the activity of cholinergic neurons [58]. Moreover, it has been reported that thioperamide significantly improves the response latency in a passive avoidance response in senescence-accelerated mice [59, 60]. Thioperamide or clobenpropit administration in mice attenuates the amnesic effects of scopolamine in the elevated plus-maze test and the step-through passive-avoidance test and improves memory [61, 62].

Attention-Deficit Hyperactive Disorder (ADHD)

ADHD is an early childhood developmental disorder with underlying motor, emotional, attention and learning alterations. Abnormalities in monoamine neurotransmitters appear to contribute significantly to the disturbances in ADHD patients [63]. The use of H_3R antagonists can be useful in attention disorders on the basis of the vigilance-promoting effects of these drugs. H_3R antagonist treatments

have procognitive properties in animal models of learning and memory, as mentioned before in this review. In some studies, impairments in cognitive processes or motor patterns are similar to those observed in ADHD. In one of the study, administration of the selective H_3R antagonist GT2016 improved the rate of acquisition of a multi-trial passive-avoidance response [64, 65].

H_3R Ligands

H_3R is an auto- and hetero- receptor, thus its activation reduces, whereas blockade increases, not only the release of histamine but also several other neurotransmitters. H_3R are not restricted to histaminergic neurons as histamine receptors are also found at various co-localized neurons [66].

H_3R agonists are mostly small molecules, having imidazole as nucleus and are derivatives of histamine. N-Methyl histamine, a potent agonist of histamine obtained by addition of methyl group at the basic amino group, is frequently used as radioligand. Imetit, immepip, impentamine, proxyfen, GT-2331 are some other H_3R agonists [66, 67]. So far, efforts to replace the imidazole-moiety in agonists have been unsuccessful [68, 69]. Addition of the methyl group in imidazole side chain results in (*R*)-α-methyl histamine, which is a typical H_3R agonist, used for the early pharmacological characterization of the H_3R [70]. Small structural changes lead to very potent ligands with selectivity for H_3R receptors, like imetit or immepip. Methylation of the piperidine nitrogen of immepip gives methimepip, currently the most potent and selective H_3R agonist. Many H_3R ligands have been developed since then and are discussed below. Thioperamide was developed as first potent selective H_3R antagonist and later clobenpropit was discovered as inverse agonist [71]. Ciproxyfan was also added to the antagonist series later [72]. The structures of the above compounds are given in (Fig. **3**).

Impentamine, a higher homolog of histamine, proxyfan and cipralisant were originally characterized to be H_3R antagonists [73]. Thioperamide was the reference H_3R antagonist for almost two decades. Newer imidazole containing H_3R ligands as potent H_3R antagonists have also been discovered. These compounds have low bioavailability, poor blood-brain barrier penetration and CYP450 inhibition due to the imidazole-moiety. The replacement of the imidazole moiety is important towards more selective and drug-like H_3R antagonists [74, 75].

Initial pharmacophore modeling for H_3R antagonists was based on a set of imidazole antagonists and consisted of two hydrophobic pockets and four hydrogen binding sites, out of which two should be in imidazole ring [76]. Based on later studies, prototype H_3 antagonist pharmacophore consisting of basic moiety separated by alkyl spacer to a central core was elucidated [77].

More recent studies shows that the H_3R antagonist pharmacophore consists of two protonation sites (i.e. basic centers) which are connected by central aromatic ring, alkyl

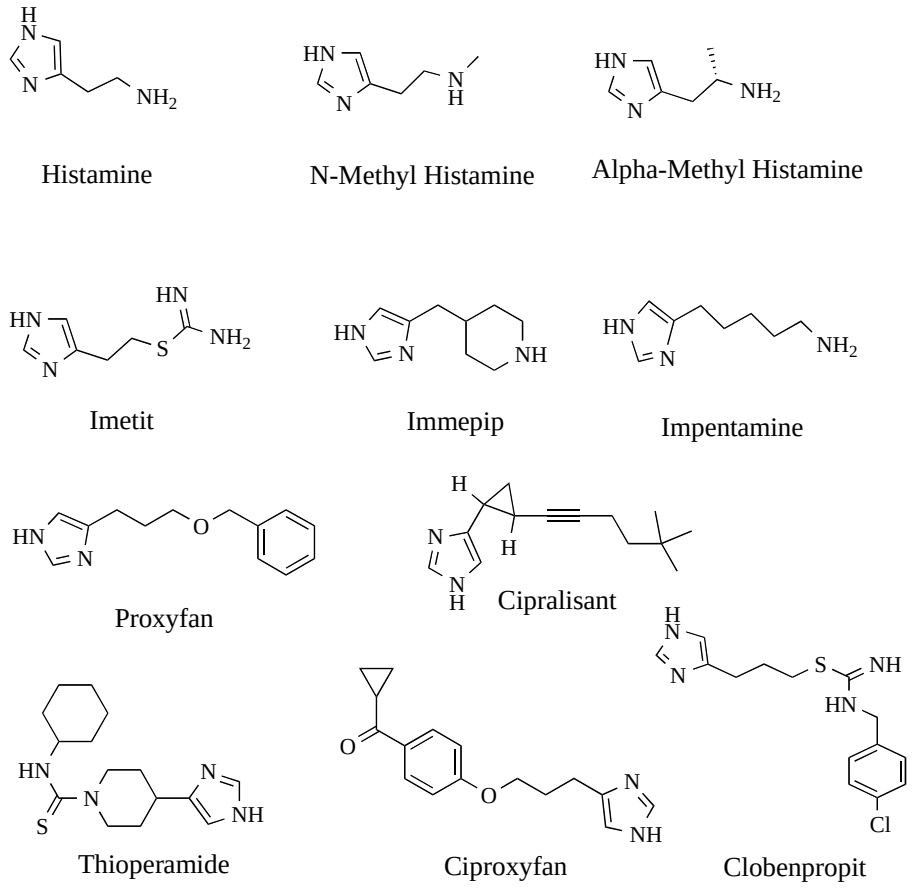

Fig. (3). Histamine and its early ligands.

spacer or hydrophobic region. The basic sites can simultaneously interact with Asp 114 and a Glu 206 which are believed to be the key residues that histamine interacts with to stabilize the receptor in the active state. The central region of these antagonists contains a lipophilic group, usually an aromatic ring that is believed to interact with several nearby hydrophobic side chains [78].

New H_3R Antagonists

The research of Mange and coworkers led to the development of potent H_3R antagonist VUF-5391. James Black foundation discovered early nonimidazole H_3R antagonist, JB-98064. Aplysamine was first to be patented by Harbor Branch Oceanographic Institution containing phenoxyalkayl, N, N-dialkyalamine fragment. Ganellin and coworkers synthesized a new series of H_3R antagonists (e.g. UCL-1972, UCL-2190, UCL-2173) for exploring the SAR of aplysamine [79, 80].

Johnson and Johnson has contributed a lot in the development of H_3 antagonists. A calcium channel blocker RWJ-20085 has been found to give high H_3R activity [81]. This compound has the N,N-dialkylamino propoxyphenyl motif of early compounds and also imidazopyrimidine motif. Optimization of RWJ-20085 led to the development of JNJ-6379490 which is having good H_3R antagonistic activity [82]. Another compound, JNJ-5207852 decreased the episodes of cataplexy in genetically narcoleptic Doberman Pinscher model. Unfortunately JNJ-5207852 showed tendency of phospholipidosis, so its development was stopped [83].

Conformational restriction to aminoalkoxy side chain of RWJ-20085 provided JNJ-7737782 which was active in rodent model of wakefulness. Another molecule with rigidified linker, JNJ-10181457 has good H_3R selectivity, brain residency and pharmacokinetic profile and increases Ach and NE levels in rat frontal cortex [84]. JNJ-17216498 is a potent orally active H_3R antagonist that has completed phase-II trial for narcolepsy [85]. RWJ-333369 has also completed phase-II clinical trials for epilepsy [86]. Structures of some of the above compounds are given in (Fig. **4**).

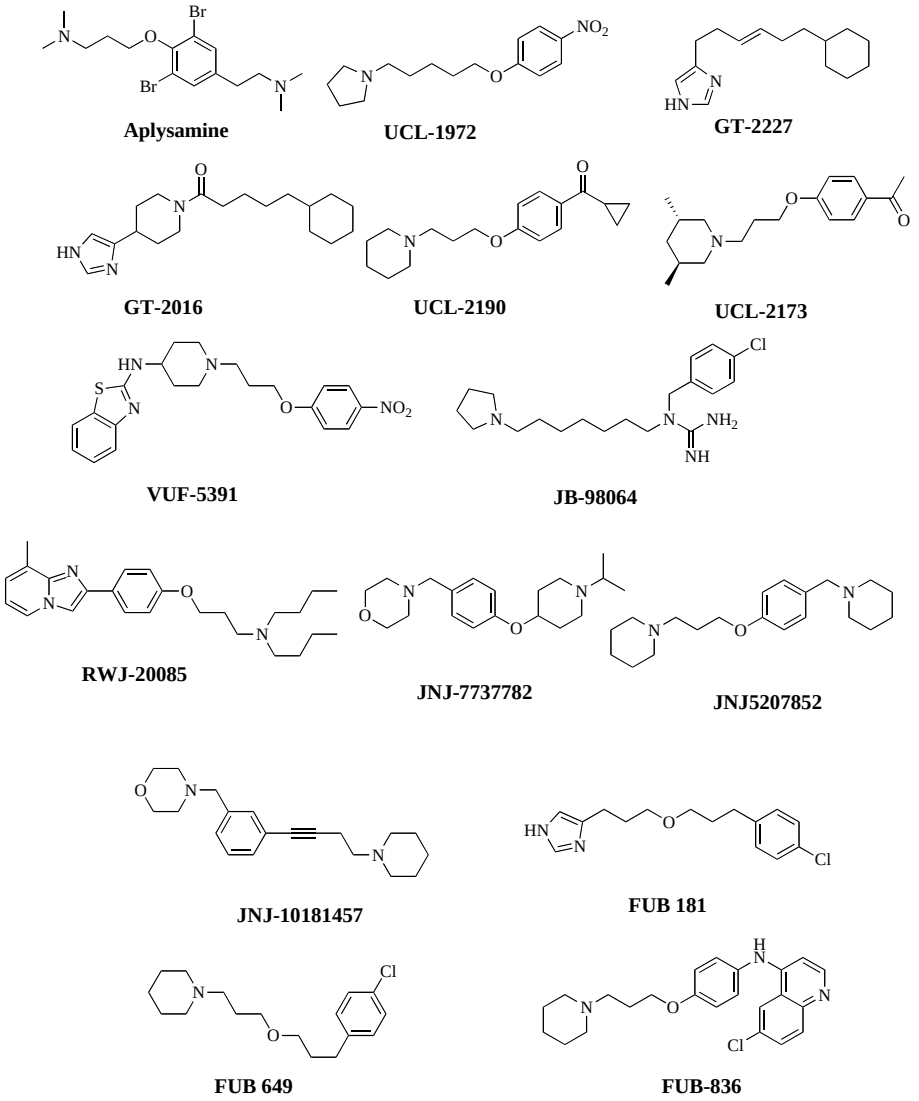

Fig. (4). Structures of histamine and its ligands from Menge and coworkers, Harbor Branch Oceanographic Institution, James Black foundation, Gliatech, Johnson & Johnson and Bioproject.

Gliatech investigated potential role of imidazole based compound GT-2331 having complex pharmacological profile. Some other compounds synthesized by Gliatech like GT-2394, GT-2227 and GT-2016 are in preclinical stage [87]. FUB UCL-INSERM Bioproject reported FUB-181, BF2.649, FUB-833 and FUB-836 as efficient and selective H_3 antagonists with increased turnover of histamine, norepinephrine and serotonin in key brain regions [88, 89]. Replacement of imidazole with piperidine gave compound BF2.649 with increased ACh and brain dopamine level in rats [90-91]. Structures of Gliatech and Bioproject compounds are given in (Fig. **4**).

Abbott also developed numerous H_3R antagonists. A phenoxy propyl piperazine analogue, A-923, was having good antagonistic potency but its bioavailability profile was poor [92]. Further lead optimization of this compound led to the development of alanine type molecules A-304121 and A-317920. Compound A-317920 showed phospholipidosis, attributed to the dibasic amine and cationic amphiphillic nature of the compound [93, 94]. A bisphenyl motif was incorporated into some compounds such as A-331440 and A-417022 but problem of poor brain penetration was observed [95, 96]. Representative antagonists from abbott are given in (Fig. **5**).

To improve absorption and drug likeliness, ABT-239 was designed as conformationally restricted analogue with propyloxy spacer tied up in benzofuran. It has excellent selectivity for H_3R and also has good bioavailability in several species of rat, dog and monkeys. Inhibition of CYP 450 was also not observed. Increased acetylcholine, dopamine and histamine levels were reported in animal models after administration of same [97, 98]. It is presently in clinical development.

Compounds A-688057 and A-687136 showed good affinity towards H_3R. Both of these compounds were effective in preclinical models of cognitive disorders. Lipophillicity was less as compared to ABT-239, so fewer incidences of phospholipidosis were observed. However, short half life due to rapid metabolism excluded the clinical development of both of these compounds [99, 100].

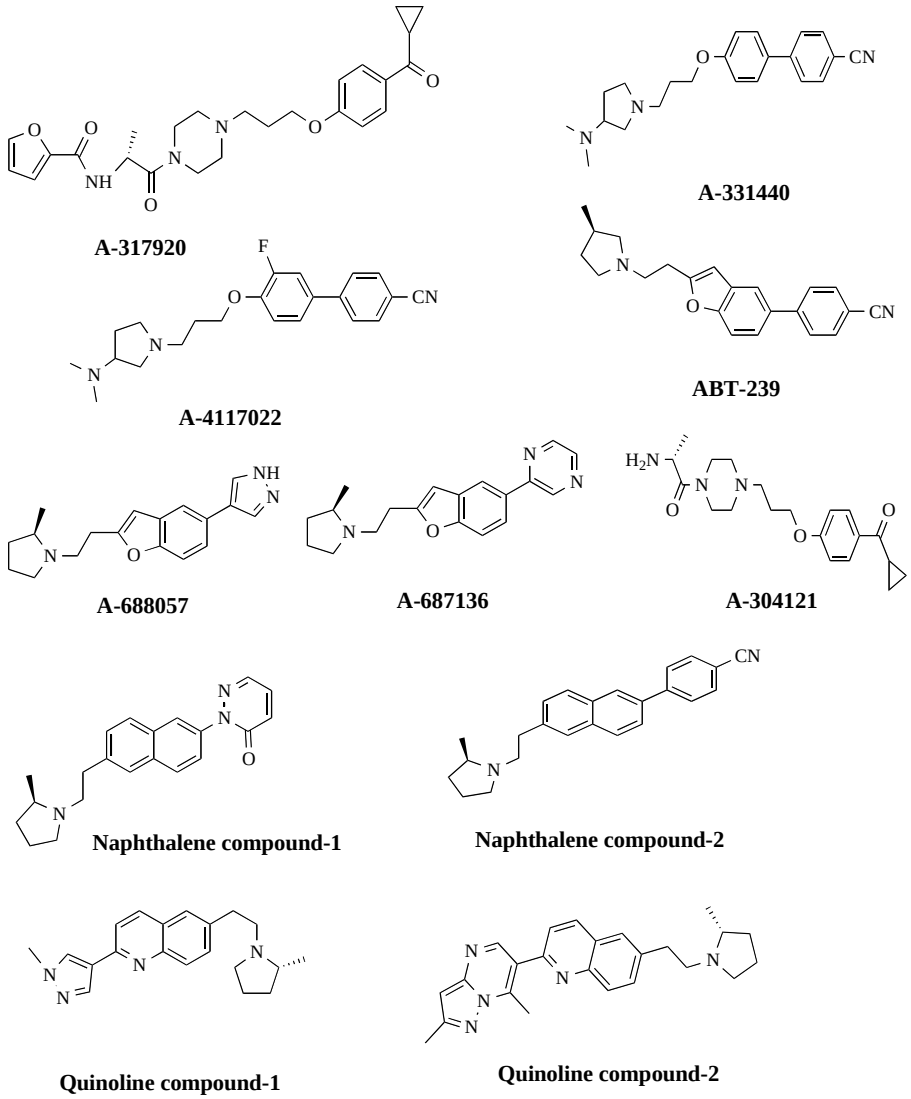

Fig. (5). New H_3R antagonists from Abbott.

Abott also synthesized naphthalene and quinoline based compounds having H_3R antagonistic profile [101]. Abott has also disclosed natural product connessine and its N- methyl D- alanine analogue as potent H_3 antagonist [102].

The quinoline compounds showed good *in vitro* potency, 90% oral bioavalability, $t_{½}$ of 5.3 hrs and good brain penetration. The development was stopped because of photo instability of salts and cardiovascular side effects [103]. The structures of some compounds synthesized by Abbott are given in (Fig. **5**).

Based on phenoxypropylamine compounds, GlaxoSmithkline have developed H_3R antagonists with tetra hydrobenzoazepine scaffold. Propyl piperidine motiff in initial compound GSK-1 could be replaced with various aryl and hetero aryl ethers. Compounds GSK-2 and GSK-207040, GSK-189254 are selective at H_3R with good brain penetration and also have good pharmacokinetic profiles [104, 105]. These compounds promote the release of acetylcholine, noradrenaline and dopamine in rat cortex [106]. Compound GSK-207040 entered in phase I trial for dementia and II for narcolepsy. GSK-239512 is also in clinical trials [107]. Some other GSK compounds, for pain and cognition activity, based on pyrazine and tetrahydrobenzoazepine motif are GSK-207040 and GSK-334429 [108]. Both these compounds are inverse agonists of H_3R. GSK-207040 has also been used for schizophrenia but not for positive symptoms. Structures of above compounds are given in (Fig. **6**).

Merck/Banyu has come in focus with new series of potent CNS penetrating quinazolinones QNZ-1, QNZ-2 and QNZ-3 [109]. In this series, compound QNZ-3 showed a favorable pharmacokinetic profile without cardiovascular and CNS toxicity. The pyrrolidinylproyloxy side chain in compound QNZ-1 was constrained as a cyclobutylpiperidinyloxy moiety in compound QNZ-2 [110]. Banyu has also disclosed quinazolinone compound, QNZ-3 with favorable results. Another H_3 antagonist MK0249 is reported to be in phase II clinical trials [111, 112]. Structures of these compounds are also given in (Fig. **6**).

Pfizer compound PF-03654746 (Fig. **6**) is in phase I trial as H_3R antagonist. This compound enhanced the release of histamine in rat prefrontal cortex. It was developed from compound by optimizing the physiological properties to avoid phospolipidosis which was observed with early analogs. On the basis of favorable results, it entered the Phase II clinical trials but later discontinued due to insomia produced as side effect [113].

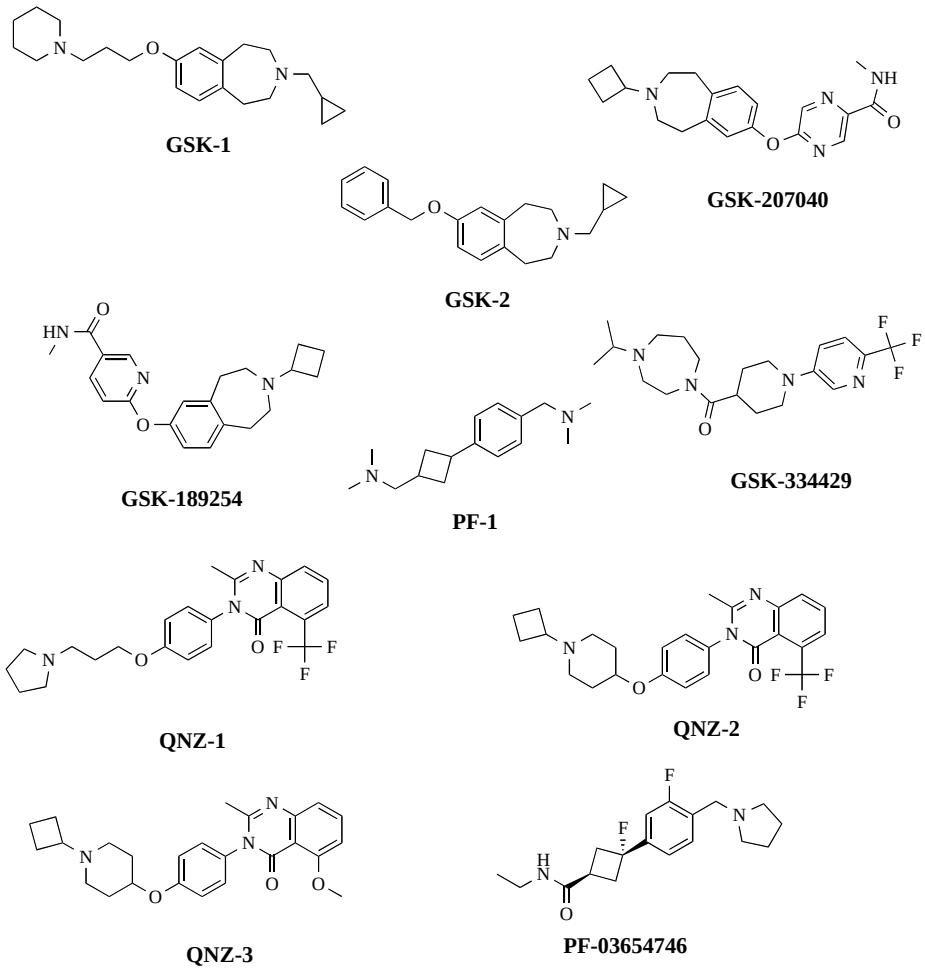

Fig. (6). New H3R antagonists from Glaxo Smithkline, Pfizer and Merck/Banyu.

Table 1. Current H_3R Antagonists with their Present Status

Sr. No.	Compound Name	Present Status	Use	References
1	BF2.649	Phase-III terminated	Narcolepsy, catalepsy	www.clinicaltrials.gov/23/12/2011
2	JNJ-17216498	Completed Phase-II	Narcolepsy	www.clinicaltrials.gov/23/12/2011
3	RWJ-333369	Phase-II completed	Epilepsy	www.clinicaltrials.gov/23/12/2011
4	ABT-239	Phase-I completed	Obesity and cognitive disorders	94,95,96
5	GSK207040	Phase-I trial for dementia, Phase-II for narcolepsy	Dementia, narcolepsy	www.clinicaltrials.gov/23/12/2011
6	GSK-239512	Phase-I completed	Alzheimer	www.clinicaltrials.gov/23/12/2011
7	PF-36504746	Phase-II completed	Schizophrenia, and ADHD	www.clinicaltrials.gov/23/12/2011

CONCLUSION

Brain histamine plays an important role in various CNS disorders. Histamine receptor antagonists cause the release of various neurotransmitters such as dopamine, gamma amino butyric acid, serotonin etc. Therefore, their role in epilepsy, schizophrenia, ADHD, narcolepsy and other central nervous system disorders is being explored. Few compounds that reached clinical trials were withdrawn due to phospholipidosis or pharmacokinetic constraints. Researchers are using the knowledge of these failures to prepare newer, selective H_3R antagonists with lesser side effects.

Current status of various representative H_3R ligands from different companies is given in Table **1**. Thus we can conclude that there is wide scope for the development of histamine H_3 receptor antagonists for the treatment of all above mentioned disorders.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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