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The histamine H3 receptor as a therapeutic drug target for CNS disorders

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The histamine H3 receptor plays a regulatory role in the pre-synaptic release of histamine and other neurotransmitters, making it an attractive target for CNS indications including cognitive disorders, narcolepsy, ADHD and pain. As more and more H3 antagonists/H3 inverse agonists progress through the clinic, knowledge is gained to define the profile of the 'ideal' compound in terms of specificity, pharmacokinetic parameters and both duration and magnitude of receptor occupancy. Whether a single compound profile for the treatment of different disorders can be defined remains to be seen.

Introduction

The histamine H3 receptor (H3R) is a G-protein-coupled receptor (GPCR) and one of the four receptors of the histamine receptor family. Histamine receptors have long been attractive drug targets, as demonstrated by the successful development of antihistamines directed at the histamine H1 receptor (for the treatment of allergic reactions) and also at the histamine H2 receptor (which, by inhibiting gastric acid secretion, revolutionised the treatment of gastric ulcers). The H3R has been identified as a mainly pre-synaptic autoreceptor, regulating the release of histamine [1,2], as well as a heteroreceptor on non-histaminergic neurons that is capable of regulating the release of many other important neurotransmitters, such as acetylcholine, norepinephrine, dopamine and serotonin (Fig. 1) [3–6].

The H3R is expressed predominantly in the central nervous system (CNS), with highest expression in the cerebral cortex, hippocampal formation, basal ganglia and hypothalamus [7,8]. These brain regions have been associated with cognition (cortex and hippocampus), sleep and homeostatic regulation (hypothalamus). In addition, H3 receptors are located in regions involved in nociception (specific thalamic areas, dorsal root ganglia and spinal cord) and therefore, might offer treatment opportunities for different modalities of pain [9].

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The physiology and pharmacology of the H3R is determined not only by its localisation and expression levels, but also by differential splicing. Today, more than 20 splice variants (isoforms) have been described but their functions have yet to be elucidated completely. Not all of these isoforms appear to be functional GPCRs but some of them might regulate functional isoforms by associating with them. A detailed review on H3R isoforms has been published recently by Bongers *et al.* [10]. Furthermore, in addition to agonist-induced signalling, the H3R is also constitutively active and capable of signalling independently of agonist both *in vitro* and *in vivo* [2], adding an additional layer of complexity.

Given its widespread distribution and its ability to affect multiple neurotransmitter systems, it is not surprising that modulation of H3R activity has been proposed for a broad range of indications such as Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), sleep disorders [11], pain and obesity. Detailed coverage of all these indications is beyond the scope of this review, for an overview the reader is referred to Wijtmans *et al.* [12]. We will instead focus on the prospects of H3R antagonists for the improvement of cognition and memory in certain disorders as well as for the treatment of sleep disorders such as narcolepsy. We will also discuss data supporting the use of H3R antagonists for pain. For these indications compounds are currently under evaluation in clinical trials. There is also information on an H3R antagonist (SCH 497079 from Schering-Plough) to enter a clinical trial for evaluating its effect on overweight and obese patients; the

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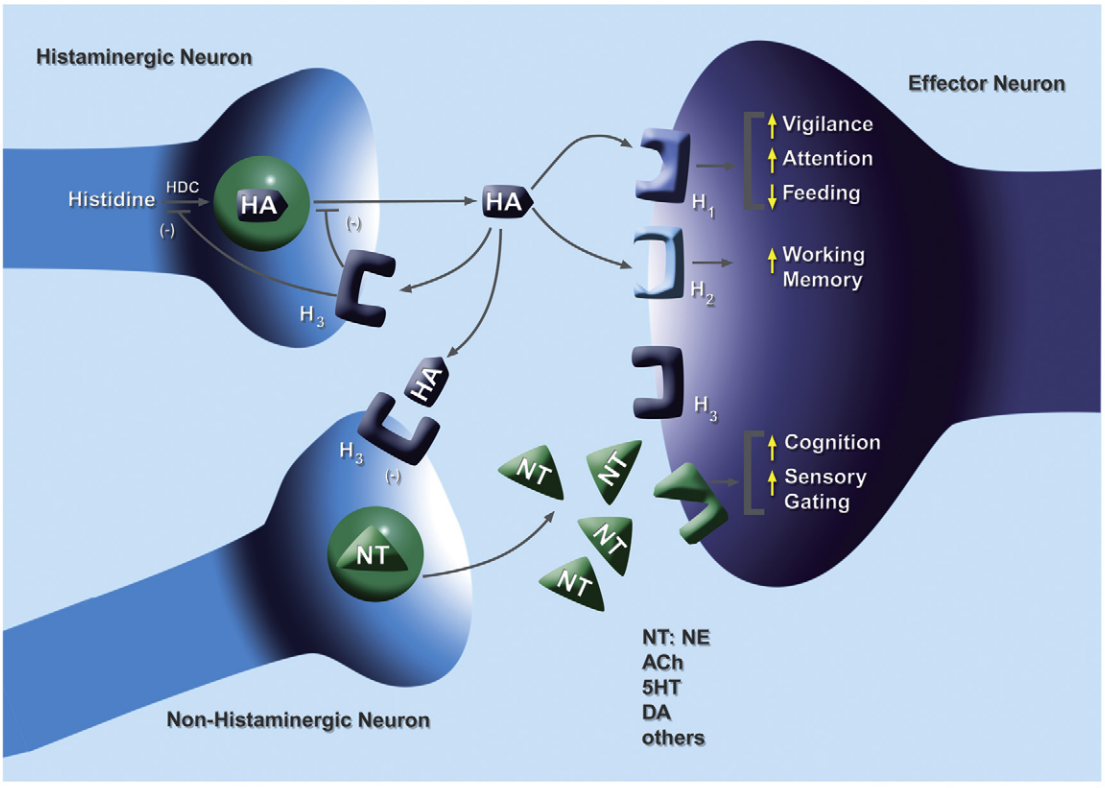


FIGURE 1

Adapted from [52]. NT: neurotransmitter; NE: norepinephrine; HA: histamine; ACh: acetylcholine; 5HT: serotonin; DA: dopamine; HDC: histidine decarboxylase.

rationale for using H3R antagonists as anti-obesity treatment is therefore briefly summarised.

Therapeutic potential of histamine H3 receptor antagonists

Cognitive dysfunction

Cognition is a highly complex phenomenon involving many different processes, most of which are still far from being understood. Many neurotransmitter systems, including acetylcholine, dopamine, serotonin and glutamate contribute to specific aspects of cognition. H3R antagonists have been found to increase not only the release of histamine, but also the release of norepinephrine, dopamine and acetylcholine [3–6], thus making H3R antagonists an attractive drug target for cognitive disorders.

For testing the potential of compounds in ameliorating cognitive dysfunction in the clinic a variety of rodent behavioural tasks can be used to analyse different domains of cognition that may have some relevance to the human disease. In most cases, the baseline performance of rodents in such tasks is close to optimal, making it difficult to demonstrate a significant improvement with pro-cognitive drugs. Indeed the effects of H3 antagonists are usually studied after normal performance is impaired with drugs such as the anticholinergic scopolamine or the NMDA antagonist dizocilpine. Impairments in spatial orientation and memory (facets that are typically observed in patients with AD) can be assessed with different paradigms such as the water maze, radial arm maze or Barnes maze. Deficits in social memory (frequently seen in AD but also of relevance to impaired cognitive performance in schizophrenia and ADHD) can be measured by a social recognition task in rodents. Impulsivity, on the contrary, which seems to be a particular problem in patients with ADHD, can be studied in the five-trial inhibitory avoidance task in spontaneously hypertensive rat (SHR) pups, as well as in the five-choice stimulus reaction time test. Executive function is a cognitive domain impaired in schizophrenic patients and is assessed using attentional set shifting assays or models of cognitive flexibility [13].

Structurally diverse H3R antagonists/inverse agonists reverse scopolamine-induced deficits in a variety of behavioural models in rodents, such as object recognition, social memory, passive avoidance, water maze, radial arm maze and Barnes maze. These findings are in line with the inhibitory influence of H3Rs on the cholinergic nucleus basalis of Meynert and the increased cortical acetylcholine levels after treatment with H3R antagonists. In agreement with this are the findings in $H3^{-/-}$ mice. Although these animals appear to learn normally, they are insensitive to the amnestic effects of scopolamine [14]. Additionally, H3R antagonists can improve passive avoidance in SHR pups and improve the performance of normal rats in an attentional set shifting paradigm (for a detailed review see [15] and references therein).

A recent article on the H3R antagonist/inverse agonist GSK207040 reported that this compound was able to reverse the isolation rearing-induced deficit in prepulse inhibition,

although it did not reverse amphetamine-induced hyperactivity [16]. Although these data are, at present, difficult to explain, it is known that a reduction in dopamine in the prefrontal cortex can induce a deficit in prepulse inhibition [17] and, as discussed above, H3R antagonists can enhance dopamine neurotransmission in the prefrontal cortex. Notably, ABT-239 has been reported not to increase dopamine release in the striatum [18] and whether H3R antagonists enhance dopamine release in other brain regions remains to be investigated.

Because H3R antagonists/inverse agonists can influence the levels of several neurotransmitters in the brain, the challenge for efficacious therapeutics will be to restore impaired neurotransmitter systems involved in diseases, without leading to an imbalance of normal brain functions.

Sleep disorders

Histamine is the major wake-promoting neurotransmitter in the CNS. It is known that histaminergic neurons display a higher firing rate during waking than during sleep [19]. Arousal during the activity phase can be augmented by increasing histamine levels through H3R blockade as demonstrated with agents such as thioperamide and ciproxifan [20]. Likewise, H3R antagonists (or inverse agonists) increase wakefulness and reduce rapid eye movement (REM) and slow-wave sleep during the sleeping phase in normal animals [21,22], an effect that is absent in $H3R^{-/-}$ mice [14]. These data suggest that H3R antagonists might be useful for disorders characterised by excessive daytime sleepiness (EDS), such as narcolepsy. Indeed, H3R antagonists reduce the number and duration of narcoleptic attacks in a canine model of narcolepsy [23]. Moreover, the first positive clinical data were recently published by Lin *et al.* showing that the H3R inverse agonist, BF2.649, significantly improved EDS parameters in comparison to placebo in a pilot phase II study [24].

Given the EEG effects of H3R antagonists, one might speculate that the pro-cognitive effects of these drugs are directly related to increased arousal. Indeed, increased arousal will improve attention, learning and memory. EEG effects do not, however, appear to be identical for all H3R antagonists and much higher doses of H3R antagonists are generally needed to affect arousal than to improve cognition [21]. On the contrary, sleep is also important for optimal functioning and memory consolidation and drugs that have a prolonged influence on arousal should be avoided. Consequently, there is a need for compounds that only affect daytime sleepiness and arousal without modifying nocturnal sleep duration. This is of particular importance when treating elderly (AD) subjects or narcoleptics, because both these patient groups already have impaired nocturnal sleep patterns.

Pain

Histamine, one of the main local inflammatory mediators, is known to be involved both in peripheral and in central nociceptive processes. Thus, when released at peripheral sites, histamine evokes pain and subsequent release of various pain-related molecules from primary afferent fibres. In the CNS, however, histamine can also affect pain processes, presumably by influencing pain perception in the thalamus and/or cerebral cortex. In a recent publication Farzin and Nosrati demonstrated that thioperamide was able to reverse imetit-induced hyperalgesia only in the late phase of the formalin model, which is thought to reflect inflammation-mediated pain, whereas histamine H1 receptors seem to be involved in both the early and late phases of this model [25]. Huang *et al.* showed that central application of thioperamide helped to increase the pain threshold in a partial nerve-ligation model, whereas systemic application reduced it [26]. These data would seem to indicate that H3R agonists may be useful for the treatment of certain types of pain stimuli and H3R antagonists for other pain stimuli [27]. Before trying to rationalise these conflicting data, it is important to realise that the agonist imetit and the antagonist thioperamide also bind to histamine H4 receptors. Using a much more selective H3R antagonist/inverse agonist, Medhurst *et al.* showed that GSK207040 significantly inhibited capsaicin-induced secondary allodynia with a maximal effect ($65 \pm 8\%$) at 1 mg/kg, compared to the vehicle group [28]. This suggests that, at least for inflammatory pain, H3R antagonists may be more beneficial than a H3R agonist, although more research is certainly needed to clarify the involvement of peripheral, spinal and brain H3Rs in various pain states.

Obesity

Patients treated with certain anti-depressants and antipsychotics show a concomitant weight gain [29] and this effect is thought to be mediated, at least in part by their ability to block H1R with high affinities [30]. Kim *et al.* demonstrated with the use of an H1R knock-out mouse that this weight gain is mediated via H1R-linked activation of hypothalamic AMP-kinase [31]. It was also shown that feeding itself increases the brain histamine level in the hypothalamus [32]; the increased histamine level can then lead to a suppression of food intake [33] demonstrating a regulatory role of the histaminergic system in food consumption. This and other evidence (for an overview see [34] as well as [35]) led to the suggestion that an increase in histamine levels by the inhibition of H3R will lead to reduced food intake. Contrary to this hypothesis Yoshimoto *et al.* showed by using a diet-induced obesity model that imetit, an H3R agonist, decreases appetite and food intake in WT but not in H3R knock-out mice [36]. It will therefore be very interesting to see whether the ongoing clinical trial with the H3 antagonist SCH 497079 will have an effect on food consumption and weight loss.

Clinical studies

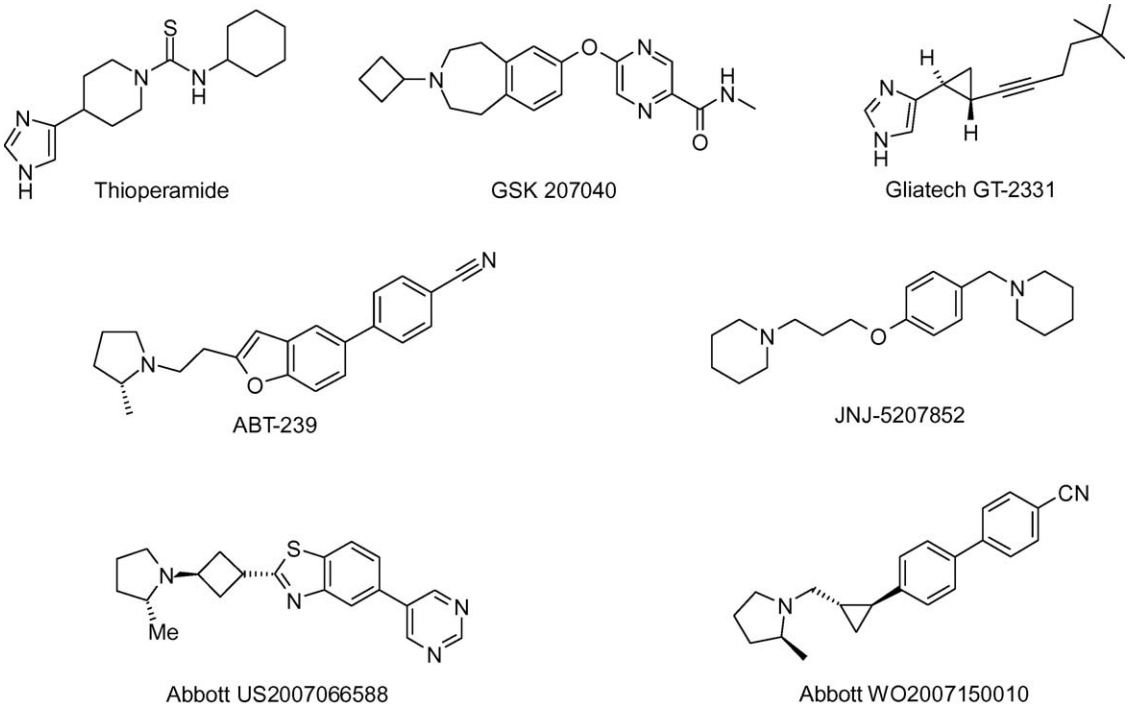
As mentioned earlier, simultaneously influencing several different neurotransmitters has to be carefully balanced and this opens up the question of whether a single compound can be developed for the diverse indications discussed, or whether compounds need to be specifically tailored for each individual indication.

For all of the indications discussed above, clinical studies have already been performed or are ongoing. Whilst publicly available data are sparse, the studies performed by GlaxoSmithKline (GSK) with their compound GSK189254 and by Merck & Co. with MK-0249 provide examples where a single compound is being evaluated in diverse indications in humans (cognition – AD and schizophrenia, narcolepsy, ADHD and pain).

GSK have presented a substantial amount of promising rodent behavioural data for their compound (GSK189254) and have even demonstrated clinical efficacy in reversing scopolamine-induced deficits in a paired-associated-learning task in humans (http://

TABLE 1

Selected H3R antagonists and representative examples from Abbott patent literature



www.gsk.com/investors/presentations/2007/neurosciences-seminar-dec07/jackie-hunter.pdf). Pre-clinically, GSK182954 has efficacy in the following tasks: passive avoidance; object recognition and attentional set shifting [37]. In addition, the same compound was also effective in certain pain models. Intriguingly, GSK recently completed a phase I study where they compared the effects of GSK189254 and the SNRI Duloxetine on electrically induced hyperalgesia. The results of this study have not been made public yet.

On the basis of publicly available data, it is too early to precisely correlate the efficacy of H3R antagonists in rodent models to the efficacy observed in humans and to thus answer the question whether H3R antagonists can be designed for the treatment of specific medical needs. On the basis of the rich literature surrounding this therapeutic target, however, we can certainly define some requirements that compounds must have to reach the clinic.

Common pre-clinical issues with H3R antagonists. What can we learn from them?

Early H3R antagonists/inverse agonists that reached the clinic were imidazole-containing compounds, such as Gliatech's clinical candidate GT-2331 (Table 1; Cipralisant, Perceptin® [38]), and have been previously reviewed [39]. The development of this class of imidazole-containing compounds was probably terminated because of the inherent risk associated with the inhibition of cytochrome P450 isoenzymes, resulting in unacceptable drug–drug interactions (DDIs) [40,41], as well as complex H3R pharmacology.

More recently, pharmaceutical and biotechnology industries have focussed efforts on the development of non-imidazole H3R antagonists, which have also been reviewed in depth elsewhere [12,39,42]. The focus of this section will be to discuss the appropriate compound and pharmacokinetic (PK) properties believed to be required for success in the clinic and to review recent pre-clinical and clinical advances with H3R antagonists.

Whilst the majority of non-imidazole classes of H3R antagonists appear not to inhibit significantly the CYP family of enzymes, many H3R antagonist programmes have reportedly suffered from significant blockade of the hERG K^+ channel [43–45] or have demonstrated the potential for phospholipidosis [43,46] or they have wrestled with P-gp substrate problems. As an example, Abbott's pre-clinical candidate ABT-239 (Table 1) is reported to exhibit strong binding to the hERG K^+ channel (K_i = 0.45 nM; 420-fold selectivity H3R/hERG) that manifested itself in a dose-dependent QTc prolongation in dog (Altenbach, personal communication) and monkey [47]. In addition, the compound was also reported to cause phospholipidosis. The combination of these two factors is probably what led to the compound's demise. For these reasons, the early assessment of all these potential liabilities in the screening cascade is recommended. Abbott's recent published patent applications, US2007066588A1 and WO2007150010A2 (a representative example is shown in Table 1) have concentrated on replacement of the 2-ethylaminobenzofuran core present in ABT-239. This modification has been reported to reduce the hERG liability [48].

Molecular modelling of the H3R has been used to rationalise the low nanomolar potency of dibasic H3R antagonists such as JNJ-5207852 (Table 1 [49]). The authors conclude that the two basic piperidine sites can simultaneously form strong piperidine salt-bridge interactions to Asp-114 on helix III and Glu-206 on helix V, which are believed to be the key residues that histamine interacts with to stabilise the active state of the receptor. Although dibasic

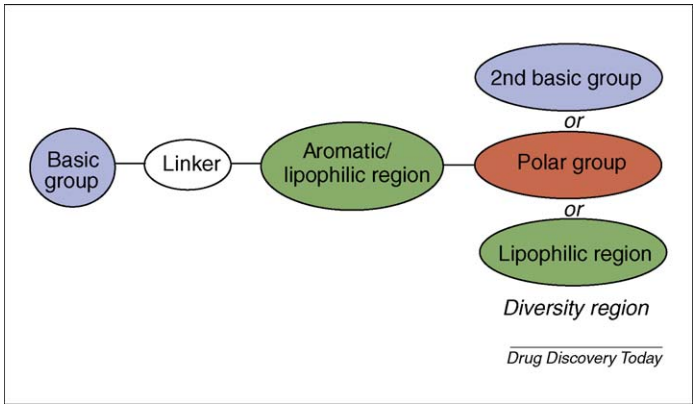


FIGURE 2

The modified pharmacophore model for non-imidazole H3R antagonists [39,60].

H3R antagonists exhibit subnanomolar potency, as well as efficacy in pharmacodynamic [50,51] and disease relevant *in vivo* models [52–54], dibasic H3R antagonists can have long brain residence times in rat [15,55,56]. A prolonged action is probably undesirable, given the wake-promoting effects of H3R antagonists and this propensity for compound accumulation is likely to have been a factor in the termination of several promising pre-clinical compounds [12,57,58]. In addition, due to their physicochemical properties these dibasic compounds often suffer from very high volumes of distribution and often cause phospholipidosis. These facets are hardly desirable in a molecule that is aiming to treat chronic illnesses.

As discussed above, one of the challenges with H3R antagonist design is overcoming the similarity between the H3 [49,59,60] and hERG [61] pharmacophores. The H3R requires a basic amine linked to an aromatic/lipophilic region that is connected to either: (i) a second basic site; (ii) a polar group or (iii) a lipophilic region (Fig. 2) [12,59,60], which makes the H3R antagonists prone to hERG inhibition and phospholipidosis [60] (Altenbach, personal communication). Therefore, every H3R antagonist programme should take these parameters into consideration as early as possible. In our own programme we were able to successfully remove activity at the hERG channel through the use of proprietary human H3R and hERG channel homology models. Both models were used to help prioritise compounds before synthesis. Furthermore, all tested Evotec compounds showed no sign of phospholipidosis.

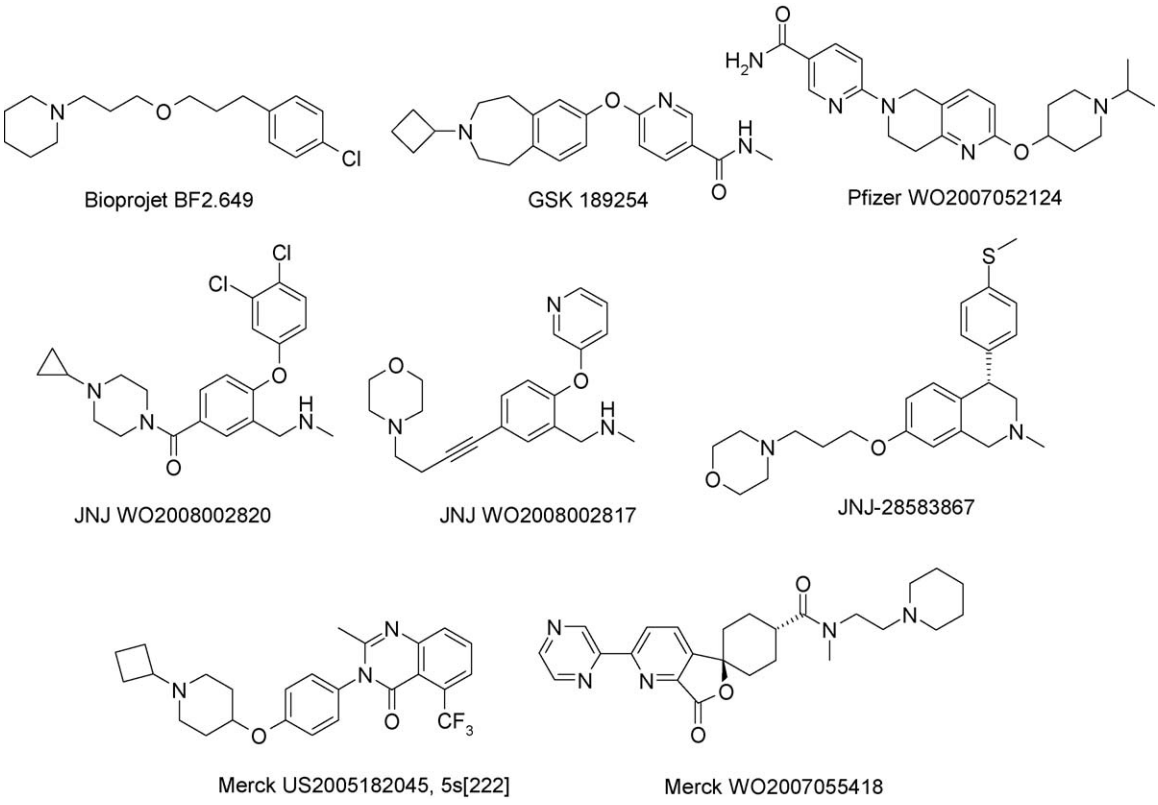
H3R antagonists/inverse agonists currently undergoing clinical evaluation

BF2.649 (tiprolisant)

Bioprojet's H3R antagonist BF2.649 (Table 2) exhibits potent binding to native human (IC_{50} = 5.3 nM), rat (K_i = 17 nM) and mouse (K_i = 14 nM) cortical H3 receptors. Further *in vitro* profiling in our laboratory (and others [15]) suggests that BF2.649 has both a CYP 2D6 liability (IC_{50} = 0.4 μM) and potent hERG K^+ channel blockade (IC_{50} = 0.49 μM). BF2.649 is also reported to have poor PK profiles in both rat and dog (5% and 2% bioavailability,

TABLE 2

H3R antagonists undergoing clinical evaluation and representative structures taken from Pfizer, Johnson & Johnson and Merck patent literature



respectively [15]). Despite these issues, BF2.649 has been extensively profiled in pre-clinical animal models [62] and progressed into the clinic. Bioprojet recently reported the first clinical evidence of efficacy with an H3R antagonist in human [24]. In a pilot, single-blind trial involving 22 subjects BF2.649 (40 mg/day) reduced the score on the Epworth Sleepiness Scale (ESS) from a baseline of 17.6 × 5.9 points and almost abolished EDS on the last day of dosing. Bioprojet are currently recruiting into a dose-range-finding phase II clinical trial for the treatment of EDS in Parkinson patients and a separate phase II trial for the treatment of schizophrenia (see http://www.clinicaltrial.gov/).

PF-03654746

Pfizer have been active in the H3 field with 18 published composition-of-matter (CoM) patent applications, covering a broad range of chemotypes (including biphenyls, spirocycles, benzimidazoles and naphthyridines). The structure of Pfizer's clinical compound PF-03654746 that recently completed a phase II allergic rhinitis study has not been disclosed. This same compound is currently being evaluated as a potential treatment for ADHD in adults. Pfizer have published one single compound patent application WO2007052124 (Table 2), suggesting this compound might be of significance.

JNJ-17216498

Johnson & Johnson (through its Belgian subsidiary Janssen Pharmaceutica) have completed a phase II clinical trial to determine the efficacy of their H3R antagonist, JNJ-17216498, in narcoleptic patients – the last status update was made in May 2008. The chemical structure of JNJ-17216498 has not been disclosed but several chemical series have been revealed in the patent literature [39]. Recent Janssen patent applications (including WO2008002820 and WO2008002817) combine dual H3R antagonist and serotonin reuptake inhibitor activity and include claims for the treatment of depression. Furthermore, pharmacological characterisation of dual H3R antagonist and serotonin reuptake inhibitor JNJ-28583867 has been disclosed [63]. Representative compounds from both patent applications and the structure of JNJ-28583867 are shown in Table 2.

MK-0249

Merck's most advanced H3R antagonist MK-0249 (structure not disclosed) which originates from its Japanese research facility (Banyu Pharmaceutical Co. Ltd) has completed phase II clinical trials to evaluate efficacy in treating AD and ADHD. Phase II studies for the treatment of cognitive deficits in schizophrenia and EDS in patients with sleep apnea are also reported. Several novel series of H3R antagonists have been reported by Banyu (Table 2). In a recent publication the development of a structurally constrained quinazolinone series is disclosed and compound 5s (Table 2) exhibiting potent hH3R activity (IC_{50} = 0.33 nM) and acceptable PK properties (33, 46 and 11% bioavailability in rat, dog and monkey, respectively) is reported as undergoing further profiling for clinical candidate selection [44].

GSK189254

GSK have published over 25 H3R antagonist CoM patent applications. Several of these applications cover the benzo[d]azepine core found in the clinical candidate GSK189254 (Table 2). In November 2006 this compound entered a phase II study to treat patients with narcolepsy. The study was reported in October 2008 to have been 'terminated' – no reason has been disclosed. GSK189254 has recently completed a phase I study in an electrical hyperalgesia model in healthy volunteers. GSK are recruiting for a phase I bridging study with GSK239512 (structure not disclosed) in patients with mild to moderate AD.

What does the future hold?

In this article, the authors have attempted to describe the promise of the H3R as a drug target, to review the current H3 clinical landscape and to highlight the many issues that have arisen during the development of H3R 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 behaviour of H3R antagonists this would seem to pose a significant challenge. The published study with BF2.649 is promising in this respect as it shows that it might be possible to reduce daytime sleep episodes without affecting nocturnal sleep significantly [24]. Caution however should be exercised given the small size of the study.

With the numerous ongoing clinical studies we face a very exciting era of H3R antagonist/inverse agonist research, as it will become possible to correlate rodent data with efficacy in humans. Current and future studies should help to determine how compounds for different indications may need to differ with respect to receptor occupancy and pharmacokinetic properties.

References

1 Arrang, J.M. *et al.* (1983) Auto-inhibition of brain histamine-release mediated by a novel class (H-3) of histamine-receptor. *Nature* 302, 832–837

2 Morisset, S. *et al.* (2000) High constitutive activity of native H-3 receptors regulates histamine neurons in brain. *Nature* 408, 860–864

3 Schlicker, E. *et al.* (1988) Histamine H3 receptor-mediated inhibition of serotonin release in the rat brain cortex. *Naunyn Schmiedebergs Arch. Pharmacol.* 337, 588–590

4 Schlicker, E. *et al.* (1989) Inhibition of noradrenaline release in the rat brain cortex via presynaptic H3 receptors. *Naunyn Schmiedebergs Arch. Pharmacol.* 340, 633–638

5 Schlicker, E. *et al.* (1993) Histamine inhibits dopamine release in the mouse striatum via presynaptic H3 receptors. *J. Neural Transm. Gen. Sect.* 93, 1–10

6 Clapham, J. and Kilpatrick, G.J. (1992) Histamine H3 receptors modulate the release of [^{3}H]-acetylcholine from slices of rat entorhinal cortex: evidence of the possible existence for H3 receptor subtypes. *Br. J. Pharmacol.* 107, 919–923

7 Drutel, G. *et al.* (2001) Identification of rat H-3 receptor isoforms with different brain expression and signaling properties. *Mol. Pharmacol.* 59, 1–8

8 Martinezmir, M.I. *et al.* (1990) Histamine receptor-H1, receptor-H2 and receptor-H3 visualized in the brain of human and nonhuman-primates. *Brain Res.* 526, 322–327

9 Cannon, K.E. *et al.* (2007) Immunohistochemical localization of histamine H-3 receptors in rodent skin, dorsal root ganglia, superior cervical ganglia, and spinal cord: potential antinociceptive targets. *Pain* 129, 76–92

10 Bongers, G. *et al.* (2007) Molecular aspects of the histamine H-3 receptor. *Biochem. Pharmacol.* 73, 1195–1204

11 Passani, M.B. *et al.* (2004) The histamine H3 receptor as a novel therapeutic target for cognitive and sleep disorders. *Trends Pharmacol. Sci.* 25, 618–625

12 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

13 Crawley, J.N. (2007) Learning and memory. *What' Wrong with My Mouse? Behavioral Phenotyping of Transgenic and Knockout Mice* (2nd edn), pp. 110–163, Wiley
14 Toyota, H. *et al.* (2002) Behavioral characterization of mice lacking histamine H-3 receptors. *Mol. Pharmacol.* 62, 389–397
15 Esbenshade, T.A. *et al.* (2008) The histamine H-3 receptor: an attractive target for the treatment of cognitive disorders. *Br. J. Pharmacol.* 154, 1166–1181
16 Southam, E. *et al.* (2009) Preclinical investigations into the antipsychotic potential of the novel H3 receptor antagonist GSK207040. *Psychopharmacology* 201, 483–494
17 Ellenbroek, B.A. *et al.* (1996) Prepulse inhibition and latent inhibition: the role of dopamine in the medial prefrontal cortex. *Neuroscience* 75, 535–542
18 Fox, G.B. *et al.* (2005) Pharmacological properties of ABT-239[4-(2-{2-[(2*R*)-2-methylpyrrolidinyl]ethyl}-benzofuran-5-yl)benzonitrile]: II. Neurophysiological characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and selective histamine H-3 receptor antagonist. *J. Pharmacol. Exp. Ther.* 313, 176–190
19 Brown, R.E. *et al.* (2001) The physiology of brain histamine. *Prog. Neurobiol.* 63, 637–672
20 Ligneau, X. *et al.* (1998) Neurochemical and behavioral effects of ciproxifan, a potent histamine H-3-receptor antagonist. *J. Pharmacol. Exp. Ther.* 287, 658–666
21 Le, S.Y. *et al.* (2008) Correlation between ex vivo receptor occupancy and wake-promoting activity of selective H-3 receptor antagonists. *J. Pharmacol. Exp. Ther.* 325, 902–909
22 Parmentier, R. *et al.* (2007) The brain H-3-receptor as a novel therapeutic target for vigilance and sleep–wake disorders. *Biochem. Pharmacol.* 73, 1157–1171
23 Leurs, R. *et al.* (2005) The histamine H-3 receptor: from gene cloning to H-3 receptor drugs. *Nat. Rev. Drug Discov.* 4, 107–120
24 Lin, J.S. *et al.* (2008) An inverse agonist of the histamine H-3 receptor improves wakefulness in narcolepsy: studies in orexin(−/−) mice and patients. *Neurobiol. Dis.* 30, 74–83
25 Farzin, D. and Nosrati, F. (2007) Modification of formalin-induced nociception by different histamine receptor agonists and antagonists. *Eur. Neuropsychopharmacol.* 17, 122–128
26 Huang, L. *et al.* (2007) Histaminergic involvement in neuropathic pain produced by partial ligation of the sciatic nerve in rats. *Reg. Anesth. Pain Med.* 32, 124–129
27 Cannon, K.E. and Hough, L.B. (2005) Inhibition of chemical and low-intensity mechanical nociception by activation of histamine H-3 receptors. *J. Pain* 6, 193–200
28 Medhurst, A.D. *et al.* (2007) Structurally novel histamine H-3 receptor antagonists GSK207040 and GSK334429 improve scopolamine-induced memory impairment and capsaicin-induced secondary allodynia in rats. *Biochem. Pharmacol.* 73, 1182–1194
29 Schwartz, T.L. *et al.* (2004) Psychiatric medication-induced obesity: a review. *Obes. Rev.* 5, 115–121
30 Richelson, E. (1978) Tricyclic antidepressants block histamine H1 receptors of mouse neuroblastoma cells. *Nature* 274, 176–177
31 Kim, S.F. *et al.* (2007) Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc. Natl. Acad. Sci. U. S. A.* 104, 3456–3459
32 Itoh, Y. *et al.* (1991) Feeding-induced increase in the extracellular concentration of histamine in rat hypothalamus as measured by in vivo microdialysis. *Neurosci. Lett.* 125, 235–237
33 Ookuma, K. *et al.* (1993) Neuronal histamine in the hypothalamus suppresses food intake in rats. *Brain Res.* 628, 235–242
34 Morimoto, T. *et al.* (2001) Brain histamine and feeding behaviour. *Behav. Brain Res.* 124, 145–150
35 Hancock, A.A. and Brune, M.E. (2005) Assessment of pharmacology and potential anti-obesity properties of H3 receptor antagonists/inverse agonists. *Expert Opin. Invest. Drugs* 14, 223–241
36 Yoshimoto, R. *et al.* (2006) Therapeutic potential of histamine H3 receptor agonist for the treatment of obesity and diabetes mellitus. *Proc. Natl. Acad. Sci. U. S. A.* 103, 13866–13871
37 Medhurst, A.D. *et al.* (2007) GSK189254, a novel H-3 receptor antagonist that binds to histamine H-3 receptors in Alzheimer's disease brain and improves cognitive performance in preclinical models. *J. Pharmacol. Exp. Ther.* 321, 1032–1045
38 Ali, S.M. *et al.* (1999) Design, synthesis, and structure–activity relationships of acetylene-based histamine H-3 receptor antagonists. *J. Med. Chem.* 42, 903–909
39 Celanire, S. *et al.* (2005) Histamine H-3 receptor antagonists reach out for the clinic. *Drug Discov. Today* 10, 1613–1627
40 Boxenbaum, H. (1999) Cytochrome P450 3A4 in vivo ketoconazole competitive inhibition: determination of K_i and dangers associated with high clearance drugs in general. *J. Pharm. Pharm. Sci.* 2, 47–52
41 Lin, J.H. and Lu, A.Y.H. (1998) Inhibition and induction of cytochrome P450 and the clinical implications. *Clin. Pharmacokinet.* 35, 361–390
42 Cowart, M. *et al.* (2004) Medicinal chemistry and biological properties of non-imidazole histamine H-3 antagonists. *Mini Rev. Med. Chem.* 4, 979–992
43 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
44 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
45 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
46 Zhao, C. *et al.* (2008) The alkaloid conessine and analogues as potent histamine H-3 receptor antagonists. *J. Med. Chem.* 51, 5423–5430
47 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
48 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
49 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
50 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
51 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
52 Esbenshade, T.A. *et al.* (2006) Histamine H-3 receptor antagonists: preclinical promise for treating obesity and cognitive disorders. *Mol. Interv.* 6, 77–88
53 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
54 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
55 Bonaventure, P. *et al.* (2007) Histamine H-3 receptor antagonists: from target identification to drug leads. *Biochem. Pharmacol.* 73, 1084–1096
56 Santora, V.J. *et al.* (2008) Novel H-3 receptor antagonists with improved pharmacokinetic profiles. *Bioorg. Med. Chem. Lett.* 18, 4133–4136
57 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
58 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
59 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
60 Lazewska, D. *et al.* (2008) Piperidine variations in search for non-imidazole histamine H3 receptor ligands. *Bioorg. Med. Chem.* 16, 8729–8736
61 Aronov, A.M. and Goldman, B.B. (2004) A model for identifying HERG K^+ channel blockers. *Bioorg. Med. Chem.* 12, 2307–2315
62 Ligneau, X. *et al.* (2007) BF2.649 [1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride], a nonimidazole inverse agonist/antagonist at the human histamine H-3 receptor: preclinical pharmacology. *J. Pharmacol. Exp. Ther.* 320, 365–375
63 Barbier, A.J. *et al.* (2007) Pharmacological characterization of JNJ-28583867, a histamine H3 receptor antagonist and serotonin reuptake inhibitor. *Eur. J. Pharmacol.* 576, 43–54