Histamine H3-receptors and sleep-wake regulation

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Invited minireview (Neuropharmacology)
Abstract

The histaminergic system fulfills a major role in the maintenance of waking. Histaminergic neurons are exclusively located in the posterior hypothalamus from where they project to most areas of the central nervous system. The histamine H3-receptors are autoreceptors damping histamine synthesis, the firing frequency of histamine neurons and the release of histamine from axonal varicosities. Importantly, this action extends also to heteroreceptors on the axons of most other neurotransmitter systems, allowing a powerful control over multiple homeostatic functions. The particular properties and locations of histamine H3-receptors provide quite favorable attributes to make this a most promising target for pharmacological interventions of sleep and waking disorders associated with narcolepsy, Parkinson’s disease and other neuropsychiatric indications.
Sleep and waking

Wakefulness and consciousness depend on perturbation of intrinsic cortical activity which is achieved through ascending activating systems taking a ventral route, the ascending reticular activating system of Moruzzi and Magoun and a dorsal route whose main station is the hypothalamus. Both pathways send direct projections to the cortex and indirect ones through the thalamus, the door to perception of sensory input. Both waking and paradoxical sleep (PS, REM) are conscious states and need activation by subcortical structures though in different ways.

Cholinergic neurons of the brainstem and the basal forebrain discharge tonically during both wakefulness and paradoxical sleep, can directly excite cortical neurons and facilitate the thalamo-cortical transmission by inhibiting the thalamic reticular sleep onset generator. Brainstem and basal forebrain cholinergic neurons are excited by glutamatergic, noradrenergic and histaminergic neurons; they are particularly important in cortical EEG arousal, but do not seem to be essential for the waking state (Szymusiak and McGinty, 1986; Lin, 2000).

Monoaminergic ascending projections containing catecholamines and serotonin are involved in sleep-waking regulation and the pathophysiology of major psychiatric disorders, schizophrenia and depression which all include disturbance in sleep-waking. Inhibition of catecholamine synthesis decreases waking and psychostimulants, like amphetamine, increase waking through accumulation of catecholamines. A lesion of the serotonergic dorsal raphe causes insomnia. These aminergic systems mediate different behavioral expressions during waking, activate immediate early genes and facilitate locomotion, perception and cognition (reviewed in Jones, 2005).
Histamine’s role in waking

The posterior hypothalamus has only recently been recognized as an important waking center in spite of early indications: destruction leads to hypersomnia. It is the only brain structure so far identified, in which lesioning or inactivation using the GABA agonist, muscimol, results in hypersomnia in several species and restores sleep in various insomniac models in the cat (reviewed in Sakai, et al., 1990; Lin, 2000). It contains the histaminergic and orexinergic neurons that have leading, distinct and complementary roles in sleep-waking regulation. The histamine system serves the maintenance of the waking state whereas the close neighbor, the orexins/hypocretins system orchestrates motor and other behavioral aspects of arousal (Anaclet, et al., 2009). Both these major waking systems and the aminergic nuclei are inhibited by GABAergic inputs from the sleep-active ventrolateral preoptic area (Sherin, et al., 1998).

Histaminergic perikarya are located exclusively in the tuberomamillary nucleus and adjacent areas of the posterior hypothalamus. Histamine neurons send inputs to various brain regions, notably those involved in the sleep–wake cycle, such as the cortex, thalamus, preoptic and anterior hypothalamus, brainstem, forebrain cholinergic and monoaminergic structures (reviewed in Schwartz, et al., 1991; Haas, et al., 2008; Haas and Panula, 2003). Identified histaminergic neurons in the mouse as well as presumed histaminergic cells in the cat discharge tonically and specifically during waking, this firing pattern being the most wake-selective identified in the brain to date (Sakai, et al., 1990; Vanni-Mercier, et al., 2003; Takahashi, et al., 2006). Histamine release is also dependent on the behavioral states and circadian clock (Haas, et al., 2008). Histaminergic neurons activate or facilitate large brain areas through postsynaptic H1- and H2-receptors, thus contributing to cortical activation. Indeed, treatments that impair histamine-mediated neurotransmission enhance cortical slow activity and increase sleep. For instance, blockade of histamine synthesis with α-
fluoromethylhistidine markedly reduces histamine levels, decreases waking and increases slow wave sleep in the cat (Lin, 2000) and rodents (Kiyono, et al., 1985; Monti, 1993; Parmentier, et al., 2002). In contrast, enhancement of histaminergic neurotransmission (e.g., by inhibiting histamine degradation using SKF91488) promotes waking (reviewed in Monti, 1993; Lin, 2000; Haas, et al., 2008). The absence of histamine synthesis in histidine decarboxylase knockout mice impairs the cortical electroencephalogram (EEG) and has deleterious effects on both sleep and wake quality, thus causing permanent somnolence and behavioral deficits. Consequently, mice that lack brain histamine are unable to remain awake when high vigilance is required, e.g. at lights off or when they are placed in a new environment (Parmentier, et al., 2002). Together, these results indicate that histaminergic neurons have a key role in maintaining the brain awake under normal conditions and in the presence of behavioral challenges. They promote wakefulness through their direct widespread projections to the cerebral cortex and indirectly via their subcortical targets in the thalamus, basal forebrain and brainstem a (Lin, et al., 1996b).

As H3-receptors provide a feedback on histaminergic neuronal somata and axons, any interference with them will also concern actions mediated by H1- and H2-receptors (Fig. 1). The H1-receptor is likely the most important physiological histamine target in the maintenance of waking. H1-receptors are found throughout the whole body and nervous system, on neurons, glia, blood cells and vessels. Particularly high densities occur in brain regions concerned with neuroendocrine, behavioral, and nutritional state control, like the hypothalamus, aminergic and cholinergic brainstem nuclei, thalamus, and cortex. It is well known that the first generation antihistamines (H1-receptor antagonists) cause sedation and drowsiness when they are used in the anti-allergic therapy. H1-receptor knockout mice share the major phenotypes of histidine decarboxylase-knockout mice and, unlike wild-type mice, they lose their waking response to H3-receptor antagonists, which relieve the autoinhibition of histamine release (Parmentier, et al., 2007).
H2-receptors mediate a potentiation of excitation, a cellular correlate of responsiveness and attention as well as long lasting synaptic plasticity through blocking a 
Ca$^{2+}$-activated potassium conductance responsible for the accommodation of firing and the long lasting (seconds) afterhyperpolarization following action potentials (Haas and Konnerth, 1983). Selective block of the H2-receptor by zolantidine, a blood-brain-barrier penetrating antagonist, does not seem to affect the sleep-wake cycle (Monti, 1993) but intracerebroventricular ranitidine (another H2-receptor antagonist) increases SWS in the cat (Lin, 2000). The long-lasting potentiating effect of H2-receptor activation on excitability of cortical neurons (Haas and Panula, 2003) likely participates in this function, at least as far as it concerns the maintenance of vigilance and attention. Finally, mice deficient in H2-receptor function exhibit selective cognitive deficits along with an impairment in hippocampal long-term potentiation (Dai, et al., 2007) and with abnormalities in nociception (Mobarakeh, et al., 2009).

**Autoreceptors and Heteroreceptors**

All aminergic systems in the nervous systems are equipped with autoreceptors serving as negative feedback to restrict the firing as well as transmitter release and synthesis at somatic and axonal locations. Such mechanisms have been first detected at the sympathetic and parasympathetic varicosities where noradrenergic $\alpha_2$-receptors and muscarinic M2-receptors block their own neurotransmitter release. At many locations the axonal varicosities of both arms of the vegetative nervous system come in close contact and can block release of the other functionally antagonistic transmitter. Similar presynaptic interactions occur ubiquitously in the central nervous system e.g. at catecholaminergic, cholinergic, serotonergic, glutamatergic, gabaergic and peptidergic terminal axons. Direct measurements of these
phenomena at single cells or even single synapses are difficult but they have been extensively studied at more macroscopic levels with push-pull, microdialysis or superfusion studies. (Schlicker, et al., 1999).

**Histamine H3-receptors**

The histaminergic H3-receptors are a particularly complex and interesting example in this field as they display constitutive activity, (Morisset, et al., 2000; Gbahou, et al., 2003; Takahashi, et al., 2003) an otherwise rarely observed phenomenon in vivo (Morisset, et al., 2000). The interaction of ligands with constitutively active receptors defines protean agonism with important functional and therapeutic implications (Leurs, et al., 2005; Stark, et al., 2001). On somata, dendrites and axons of TMN neurons, H3-autoreceptors inhibit cell firing (Stevens, et al., 2001, Fig. 2), as well as histamine synthesis and release from varicosities (Arrang, et al., 1987). As presynaptic heteroreceptors H3-receptors control the release of a variety of other neurotransmitters involved in sleep-waking regulation, including biogenic amines (Schlicker, et al., 1999), acetylcholine (Passani, et al., 2004), glutamate (Doreulee, et al., 2001), GABA and peptides (Pillot, et al., 2002) (Fig. 1).

The location of H3-receptors in areas receiving histaminergic innervation matches their role as auto- and heteroreceptors. High densities are found in the hypothalamus, the cerebral cortex, hippocampus, amygdala, nucleus accumbens, striatum, olfactory tubercles, cerebellum, substantia nigra, and brainstem. Loss of H3-receptors function in knockout-mice is associated with behavioral state abnormalities, reduced locomotion (Toyota, et al., 2002), a metabolic syndrome with hyperphagia, late-onset obesity phenotypes (Yoshimoto, et al., 2006; Tokita, et al., 2006) and an increased severity of neuroinflammatory diseases, in keeping with data from genetic linkage studies.
The sleep-wake cycle of H3-receptor knockout mice show clear signs of enhanced histamine neurotransmission and vigilance, notably a greater extent of waking during behavioral tasks, including environmental change, locomotion, and motivation tests. On the other hand, they display deficient waking in the absence of stimuli, probably due to a desensitization of postsynaptic histamine receptors under constant histamine release (Gondard, et al., 2010). These sleep-wake characteristics and the obesity phenotypes reported in this model suggest that chronic enhancement of histaminergic neurotransmission eventually compromises the whole brain arousal system, leading to sleep-wake, behavioral, and metabolic disorders. With its unique pharmacological properties the H3-receptor is a major target for development of drugs against various disorders of the brain (Passani, et al., 2004; Leurs, et al., 2005).

**Mechanisms of H3-receptor actions**

Autoreceptor feedback in other systems is often achieved through G-protein coupled receptors directly mediating activation of potassium channels, causing hyperpolarisation and inhibition. Histamine neurons display a pacemaker firing pattern that depends on a number of intrinsic properties: dendritic Ca\(^{2+}\) mediated prepotentials, decisive in this process, are suppressed by H3R activation. The H3-receptors also cause inhibition of release at axonal varicosities by blocking Ca\(^{2+}\)-channels, that are essential for triggering the transmitter exocytosis. Thus the firing of histamine neurons is inhibited in vitro by H3-receptor agonists such as \(\alpha\)-methylhistamine, and enhanced by H3-receptors antagonists (Fig. 1 and 2). Similarly, H3-receptor ligands modulate the firing rate of histamine cells in vivo (Vanni-Mercier, et al., 2003).
The basal ganglia are concerned with motor programming, implicit learning and addictive behavior that are all behavioral state-dependent. H3-receptors are found at high densities in the basal ganglia, especially on the gabaergic medium spiny neurons (Ryu, et al., 1994; Goodchild, et al., 1999). H3-receptor mRNAs in the cortex and in the substantia nigra pars compacta indicate the presence of H3 heteroreceptors on the major inputs to the striatum. H3-receptor activation inhibits glutamate release from rat striatal synaptosomes. In slices from the striatum glutamatergic transmission and synaptic plasticity are reduced by H3-receptor activation (Doreulee, et al., 2001). This action is severely compromised in an animal model of hepatic encephalopathy along with abnormalities of basal ganglia output function and (sleeping) behavior (Sergeeva, et al., 2005). The dopaminergic nigrostriatal input that controls glutamatergic excitation (and the drive of the principal neurons) is regulated by histamine H3-heteroreceptors.

The hippocampus receives two histaminergic fiber bundles, through the fornix and a caudal route. In spite of a rather weak innervation histamine actions are quite remarkable in this structure. The input pathway to the dentate gyrus from the entorhinal cortex is suppressed by H3-receptor activation. Stimulation of the TMN during exploratory behavior also inhibits transmission here and this effect is blocked by intracerebroventricular injection of an H3-receptor antagonist (Brown and Haas, 1999).

**Sleep-wake disorders**

The sleep-wake cycle may be disturbed in many different ways, for instance with pathologies termed somnolence, insomnia, hypersomnia and narcolepsy. The latter is a sleep disorder characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone during waking) and narcoleptic episodes (i.e., direct onset of paradoxical sleep from wake).
Narcolepsy affects 0.05-0.2% of the general population, but other sleep-wake disorders (e.g. somnolence) affect a large number of individuals. The causes may be identified pathologies like obstructive sleep apnoea, neurological and neuropsychiatric disorders, such as Parkinson’s disease, Alzheimer’s disease and depression or related to circumstances linked to lifestyle (e.g., stress, jet lag and daytime somnolence due to voluntary sleep restriction from nocturnal jobs or overwork). According to a recent inquiry from the USA, 60% of adults experience sleep problems and believe that this affects their quality of life. 10.2% of the population consider themselves nocturnal insomniacs (causing daily somnolence) and take sedatives at least once a week, whereas 3.2% consider themselves hypersomniacs.

Somnolence is the direct cause of a large number of road and work accidents and several disasters in history. Because of this large prevalence, sleep-wake disorders cause a high annual cost to our society, estimated at $50-100 billion in the USA (National Commission on sleep Disorders Research. Executive Summary and Executive Report. Bethesda MD: NIH, 1993 and University of Maryland, Sleep Disorders Center: http://www.umm.edu/sleep/sleep_dis_main.htm).

**H3-receptors: targets for arousal control and treatment of sleep-wake disorders**

Since H3-receptors control the release, synthesis and turnover of histamine and the neuronal activity of histaminergic cells (Arrang, et al., 1983; Schwartz, et al., 1991; Vanni-Mercier, et al., 2003), it was hypothesized, soon after the discovery of the H3-receptor and its ligands, that the sleep–wake cycle is modulated through H3-receptors which may thus constitute a brain target for the treatment of sleep-wake disorders (Lin, et al., 1990). Consistent with this hypothesis, early studies in cats showed that sleep increased or decreased following administration of H3-receptor agonists or antagonist/inverse agonists, respectively. Thioperamide, an imidazole H3-receptor antagonist, promoted cortical activation and waking
while α-methylhistamine, a chiral H3-receptor agonist and BP2-94, another H3-receptor agonist, enhanced cortical slow activity and increased slow wave sleep (Lin, 2000; Lin, et al., 1990). Similar results were obtained using H3-receptor agonists or antagonists in mice, rats and guinea pigs (Monti, 1993; McLeod, et al., 1998; Parmentier, et al., 2002), although the effect of H3-receptor agonists appeared to be compound- and species- dependent (Lamberty, et al., 2003; Hancock, 2006).

In midbrain-transectioned cats in which the cerebral cortex presents continuous high voltage slow activity without spontaneous activation similar to that seen in coma, the use of small doses of ciproxifan (another H3-receptor antagonist/inverse agonist) activates histamine neurons and restores a sustained cortical activation (Lin, 2000).

The marked effects of H3-receptor ligands on sleep-wake cycles in animals support their potential therapeutic role in human sleep-wake disorders, notably the use of H3-receptor antagonist/inverse agonists to improve somnolence and vigilance deficiency of diverse pathophysiological origins. For this purpose, their effects have been compared to those of current wake-promoting substances such as modafinil (Bastuji and Jouvet, 1988; Lin, et al., 1996a) and classical psychostimulants like amphetamine and caffeine in the mouse: thioperamide and ciproxifan enhance cortical activation and waking and, like modafinil, but unlike amphetamine and caffeine, their waking effects were not accompanied by behavioral excitation and sleep rebound. Similar results are seen with the more recently-identified H3-receptor antagonists/inverse agonists such as BF2.649 (Pitolisant), S41150, GSK-189254 and JNJ-5207852 (Barbier, et al., 2004; Ligneau, et al., 2007b; Zhang, et al., 2007; Guo, et al., 2009). Moreover, all wake-promoting agents cause a clear suppression of cortical slow waves (δ and slow θ bands, mainly 0.8-5 Hz), whereas only H3-receptor inverse agonists like ciproxifan enhance cortical fast rhythms (β and γ bands, 20-60 Hz) (Parmentier, et al., 2007).

Because the occurrence of cortical fast rhythms is closely associated with the higher mental activities such as attention, alertness, and learning, these results indicate that waking
elicited by H3-receptor inverse agonists presents a high level of vigilance and that the histaminergic system plays a role not only in waking, the prerequisite for all other higher brain functions, but also in some cognitive processes. Thus, potential benefits of H3-receptor antagonists/inverse agonists are not limited to promoting wakefulness, as they may also improve vigilance and cognitive outputs. Many more recently-identified compounds from different pharmaceutical companies such as BF2.649 (Pitolisant), ABT-239, GSK-189254, JNJ-10181457 (Fox, et al., 2003; Fox, et al., 2005; Medhurst, et al., 2007; Bonaventure, et al., 2007; Ligneau, et al., 2007b; Esbenshade, et al., 2008) confirm the procognitive properties of H3-receptor antagonists/inverse agonists. It is interesting to note here that the doses of H3-receptor inverse agonists required to invoke wakefulness are often somewhat higher than those used to improve cognition. This suggests that higher H3 receptor occupancy (estimated >80%) is probably required for wake induction than for wake maintenance and cognitive improvement (Medhurst, et al., 2007; Le, et al., 2008; Guo, et al., 2009). Moreover, in these animal studies with doses inducing or improving wakefulness, no clear signs of CNS side-effects such as hyperactivity or abnormal excitation were reported. The histaminergic system, although excitatory with respect to waking, acts rather anticonvulsive as a whole, H1R antagonists are proconvulsive in children (discussed in Haas et al., 2008). Thus, H3R antagonism, through the resulting enhancement of histaminergic tone, could also be anticonvulsive (Yokoyama et al., 1994). In contrast to the antagonists/inverse agonists, the H3-receptor agonist imetit enhances sleep and dose-dependently attenuates ciproxifan-induced waking in mice, indicating that the effects of both ligands are mediated by H3-receptors (Parmentier, et al., 2007). Unlike the procognitive activity of antagonists, H3-receptor agonists appear to possess anxiolytic-like profiles (Yokoyama, et al., 2009) and thus would be expected to improve sleep after stress.

In spite of the high complexity and heterogeneity of the H3-receptor, including sequence differences across species, multiple splice isoforms and constitutive activity
(Morisset, et al., 2000; Hancock, 2006), various H3-receptor inverse agonists of distinct chemical designs all promote wakefulness in a wide range of animal models. Studies using knockout mice have allowed further characterization of the wake-promoting effects of H3-receptor antagonists/inverse agonists in order to assess whether they are mediated by the histamine neurotransmission or by the H3-receptor regulated release of other neurotransmitters also involved in arousal, such as noradrenalin, dopamine, acetylcholine, 5-HT and some neuropeptides. Hence, it was shown that ciproxifan or thioperamide, which elicit marked cortical activation and waking in normal animals; produce no effect at all in either histidine-decarboxylase knockout mice or H1- or H3-receptor knockout mice whereas the waking effect persists in H2-receptor knockout mice (Toyota, et al., 2002; Parmentier, et al., 2007; Parmentier, et al., 2002). This is in keeping with the early finding that the waking effect of H3-receptor inverse agonists is significantly attenuated by the H1-receptor antagonist mepyramine (Lin, et al., 1990).

All these results validate the hypothesis that H3-receptor inverse agonists, through disinhibition of H3-autoreceptors, enhance synaptic histamine release that in turn activates postsynaptic H1-receptors and promotes waking. Interestingly, amphetamine and modafinil, despite their causing potent arousal, appear unlikely to depend on a histaminergic mechanism as their effects are intact in histidine decarboxylase knockout mice (Parmentier, et al., 2007). Furthermore, neither modafinil nor psychostimulants, but only ciproxifan induces expression of c-fos (an immediate early gene marker of neuronal activation) in histamine neurons in the cat tuberomamillary nucleus (Lin, et al., 1996a; Lin, 2000; Vanni-Mercier, et al., 2003) when c-fos expression is examined just before the onset of the sustained waking state. These data thus distinguish two classes of wake-improving agents: one acting through histamine, the other via non-histaminergic mechanisms. Whereas the wake-promoting property of H3-receptor inverse agonists is most likely dependent on H3-autoreceptor mediated modulation of histaminergic neurotransmission, their procognitive activity appears to involve not only the
histaminergic, but also other neurotransmitter systems which are controlled by H3-heteroreceptors and play important roles in cognition such as the cholinergic neurons (Khatib, et al., 1995; Lin, et al., 1996b; Passani, et al., 2004; Jones, 2005; Bonaventure, et al., 2007; Ligneau, et al., 2007a; Parmentier, et al., 2007; Haas, et al., 2008).

Since the proposition of H3-receptors as potential therapeutic targets for vigilance and sleep-wake disorders (Lin, et al., 1990), considerable effort has been made world-wide to identify clinically suitable H3-receptor antagonists/inverse agonists. This has led to the identification of highly potent and selective compounds with good bio-availability/brain penetration and low toxicity. These second generation compounds have confirmed the preclinical data obtained with early agents but without many of their deficiencies. A large number of compounds have recently entered preclinical and clinical trials and are being tested in sleep-wake and cognitive disorders, notably in narcolepsy: ABT -288, BF2.649 (tiprolisant or pitolisant), GSK189254, GSK239512, JNJ-17216498, MK-0249, MK-3134 and PF-03654746 (Ligneau, et al., 2007b; Medhurst, et al., 2007; Bonaventure, et al., 2007; Esbenshade, et al., 2008) (see http://clinicaltrial.gov). Their potential indications and status in clinical trials are summarized in Table 1.

So far the only clinically suitable wake-promoting agent is modafinil (Bastuji and Jouvet, 1988; Lin, et al., 1996a), now used in sleep medicine world-wide. In orexin knockout narcoleptic mice, however, modafinil improves waking but the narcoleptic episodes persist. Unlike modafinil, BF2.649 (pitolisant) improves waking and suppresses narcoleptic episodes as well. Interestingly, modafinil amplifies the wake-promoting and anti-narcoleptic effects of pitolisant, suggesting a synergy that could be clinically useful (Fig. 3. Lin, et al., 2008). Such a simultaneous use of two wake-promoting agents appeared to be well tolerated by the animals as no clear signs of CNS over-excitation or hyperactivity were noted. This synergy involves a dual mechanism leading to strong activation of histamine neurons: pitolisant reverses the constitutive activity of the H3-receptors, i.e. of a potent “brake” on histamine
release (Morisset, et al., 2000) whereas modafinil reduces GABA outflow in the posterior hypothalamus (Ferraro, et al., 1996; Lin, et al., 2008), thereby disinhibiting histaminergic neurons. A similar anti-narcoleptic effect is seen with other H3-receptor inverse agonists. For instance, GSK189254 suppresses narcoleptic episodes in orexin knockout mice and, unlike psychostimulants which develop tolerance, repeated dosing reinforces selectively its anti-narcoleptic effect in orexin-knockout mice (Guo, et al., 2009). Furthermore, JNJ-10181457 decreases cataplexy in Doberman dogs (Bonaventure, et al., 2007). Following these promising preclinical data, a recent clinical trial phase II proof of concept study conducted in narcoleptic patients shows that pitolisant significantly improves the excessive daytime sleepiness (Lin, et al., 2008). The efficiency of H3-receptor inverse agonists on human cataplexy remains to be evaluated. In a phase III clinical trial, pitolisant also improves somnolence and motor parameters in Parkinson’s disease (Arnulf and Leu-Semenescu, 2009). Because cognitive disorders such as schizophrenia, attention deficit hyperactivity disorder and Alzheimer’s disease are often associated with vigilance impairment which, in turn, may aggravate the patients’ cognitive defects, clinical trials are underway to determine the potential utility of H3-receptor antagonists/inverse agonists.

As the purpose of such a therapy is to improve daytime waking, vigilance and cognition without disturbing patients’ nocturnal sleep, the choice of compounds with reasonable half-life and therapeutic dose window would be particularly important and requires individualization in order to prevent possible peripheral and CNS side-effects such as over-excitation (e.g. insomnia). This therapeutic approach is based on a clearly defined molecular target, the H3-receptor, and the well-established role of histaminergic neurons in qualitative and cognitive aspects of waking (Lin, 2000; Ligneau, et al., 2007b; Passani, et al., 2004; Anaclet, et al., 2009). Moreover, a defect in the histaminergic system is the direct cause of somnolence of diverse pathological origins in animals and patients with sleep disorders (Nishino, et al., 2009; Parmentier, et al., 2002; Kanbayashi, et al., 2009). Therefore H3-
receptor inverse agonists provide a most promising therapy for unwanted (pathological) somnolence.
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hypothalamus in the regulation of wakefulness and paradoxical sleep, in The Diencephalon


Footnote

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Legends for figures

Fig. 1. Histaminergic neurons and their targets. H3 receptors on histaminergic somata (left, auto) and their axons (auto), as well as on the axons of other neuronal systems (H3 heteroreceptors on glutamatergic, cholinergic, catecholaminergic, serotonergic, GABAergic, peptidergic cells). H1 and H2 receptors on a target cell body. Release of histamine from dendritic and axonic vesicles. Modified from Nature Reviews Neuroscience 4:121-130, Haas HL and Panula P, The role of histamine and the tuberomamillary nucleus in the nervous system, copyright 2003, Macmillan Magazines Ltd.

Fig. 2. Recording from histaminergic neuron in the tuberomamillary nucleus in vitro.

The action potential firing at 2 Hz is doubled under thioperamide (H3R antagonist) that removed the autoinhibition through H3-receptors. Right: whole-cell recording from histaminergic neuron illustrates Ca^{2+} inward current in response to a positive voltage command (from the membrane potential -50 mV to 0 mV). This Ca^{2+} current is markedly reduced by R-α-methylhistamine (H3R agonist). Modified from Nature Reviews Neuroscience 4:121-130, Haas HL and Panula P, The role of histamine and the tuberomamillary nucleus in the nervous system, copyright 2003, Macmillan Magazines Ltd.

Fig. 3. Effects of tiprolisant and/or modafinil on sleep-wake cycles and narcoleptic episodes (DREM) in orexin/- mice. Note that 1) DREM episodes occur during lights-off; 2) Both tiprolisant (20 mg/kg) and modafinil (64 mg/kg) enhance waking (W) and decrease slow wave sleep (SWS) and paradoxical (REM) sleep; 3) Tiprolisant reduces DREM episodes whereas modafinil allows them to persist; and 4) co-administration of tiprolisant and
modafinil results in a greater increase in W and a total suppression of DREM episodes.

Table 1. H3-receptor inverse agonists/antagonists: indications and clinical studies.

<table>
<thead>
<tr>
<th>Name</th>
<th>Potential indication</th>
<th>Status of clinical trial</th>
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<tr>
<td>ABT-288</td>
<td>AD &amp; schizophrenia</td>
<td>Phase II</td>
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<tr>
<td>BF2.649 (Pitolisant)</td>
<td>Somnolence &amp; EDS in narcolepsy &amp; Parkinson’s disease</td>
<td>Phase III</td>
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<td></td>
<td>Epilepsy</td>
<td>Phase II</td>
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<td></td>
<td>Cognitive impairments</td>
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<td>MK-3134</td>
<td>Sleep &amp; cognitive disorders</td>
<td>Phase I</td>
</tr>
<tr>
<td>PF-03654746</td>
<td>Narcolepsy &amp; cognitive disorders</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; ADHD, attention deficit hyperactivity disorder; EDS, Excessive daytime sleepiness.
Fig. 1

- H3R auto
- dendrites
- H1R
- H2R
- histaminergic axon
- glutamatergic, cholinergic, aminergic, GABAergic, peptidergic axons
- hetero
histaminergic neuron:

firing 2Hz

thioperamide 1 μM

Ca\(^{2+}\) - current

R-α-methyl histamine

control

Fig. 2
Fig. 3

vehicle

modafinil

tiprolisant

modafinil + tiprolisant