Histamine H₃ Receptors and Sleep-Wake Regulation

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ABSTRACT

The histaminergic system fulfills a major role in the maintenance of waking. Histaminergic neurons are located exclusively 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. It is noteworthy that this action also extends 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 that 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 (REM) are conscious states and need activation by subcortical structures, although 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 electroencephalogram 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, all of which include disturbance in sleep-waking. Inhibition of catecholamine synthesis decreases waking, and psychostimulants, such as amphetamine, increase waking through accumulation of catecholamines. A lesion of the serotoninergic 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

ABBREVIATIONS: REM, rapid eye movement; DREM, direct transition from wake to REM sleep; SWS, slow wave sleep; CNS, central nervous system; SKF91488, 4-(N,N-dimethylamino)butylisothiourea; BP2-94, (R)-(-)-2-[(N-[1-(1H-imidazol-4-yl)-2-propyl]mimino)phenylethyl]phenol; BF2.648, 1-[3-[4-(chlorophenyl)propoxy]propyl]piperidine hydrochloride; GSK-189256, 6-[3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yloxy]-N-methyl-3-pyridinecarboxamide; JN-5207882, 1-[3-[4-(piperidin-1-ylmethyl)phenoxo]propyl]piperidine; ABT-239, 4-[2-[(2R)-2-methylpropyl]pyrrolidin-1-yl]benzofuran-5-yl]benzonitrile; JNJ-10181457, 4-[3-(4-piperidin-1-ylbut-1-ynyl)phenoxo]propyl]piperidine; JNJ-5207852, 1-[3-[4-(piperidin-1-ylmethoxyl)phenyl]propyl]piperidine; ABT-239, 4-[2-[(2R)-2-methylpropyl]pyrrolidin-1-yl]benzofuran-5-yl]benzonitrile; JNJ-10181457, 4-(3-(4-piperidin-1-ylbut-1-ynyl)phenyl)morpholine; FF-03654746, (1R,3R)-N-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]cyclobutane-1-carboxamide.
The H1 receptor is probably the most important physiological histamine target in the maintenance of waking. H1 receptors contribute to cortical activation. Indeed, treatments that contribute to histamine levels, decreases waking, and increases slow wave sleep in the cat (Lin, 2000) and rodents (Haas et al., 2008). Identified histaminergic neurons in the mouse and 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 also depends 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 4-((N,N-di-methylaminobutylisothiourea (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 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 (Lin et al., 1996b).

Because H3 receptors provide feedback on histaminergic neuronal somata and axons, any interference with them will also concern actions mediated by H1 and H2 receptors (Fig. 1). The H3 receptor is probably the most important physiological histamine target in the maintenance of waking. H3 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, such as the hypothalamus, aminergic and cholinergic brainstem nuclei, thalamus, and cortex. It is well known that the first-generation antihistamines (H2 receptor antagonists) cause sedation and drowsiness when they are used in antiallergic 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, and long-lasting synaptic plasticity through blocking a Ca2+-activated potassium conductance responsible for the accommodation of firing and the long-lasting (seconds) afterhyperpolarization after 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 slow wave sleep (SWS) in the cat (Lin, 2000). The long-lasting potentiating effect of H2 receptor activation on the excitability of cortical neurons (Haas and Panula, 2003) probably 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 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 were first
detected at the sympathetic and parasympathetic varicosities where noradrenergic \( \alpha_2 \) receptors and muscarinic \( M_2 \) 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 \( H_3 \) Receptors**

The histaminergic \( H_3 \) receptors are a particularly complex and interesting example in this field because 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 protein agonism with important functional and therapeutic implications (Stark et al., 2001; Leurs et al., 2005). On somata, dendrites, and axons of tuberomammillary nucleus neurons, \( H_3 \) 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 \( H_3 \) 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), and GABA and peptides (Pillot et al., 2002) (Fig. 1).

The location of \( H_3 \) receptors in areas receiving histaminergic innervation matches their role as autoreceptor 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 \( H_3 \) 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 (Tokita et al., 2006; Yoshimoto et al., 2006), and an increased severity of neuroinflammatory diseases, in keeping with data from genetic linkage studies.

The sleep-wake cycle of \( H_3 \) receptor knockout mice shows 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, the mice display deficient waking in the absence of stimuli, probably caused by 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 \( H_3 \) 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 \( H_3 \) Receptor Actions**

Autoreceptor feedback in other systems is often achieved through G protein-coupled receptors directly mediating activation of potassium channels, causing hyperpolarization 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 \( H_3 \) receptor activation. The \( H_3 \) 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 \( H_3 \) receptor agonists such as \( \alpha \)-methylhistamine and enhanced by \( H_3 \) receptors antagonists (Fig. 1 and 2). Likewise, \( H_3 \) 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. \( H_3 \) 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). \( H_3 \) receptor mRNAs in the cortex and the substantia nigra pars compacta indicate the presence of \( H_3 \) heteroreceptors on the major inputs to the striatum. \( H_3 \) receptor activation inhibits glutamate release from rat striatal synaptosomes. In slices from the striatum glutamatergic transmission and synaptic plasticity are reduced by \( H_3 \) 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 \( H_3 \) 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 \( H_3 \) receptor activation. Stimulation of the tuberomammillary nucleus
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 0.5 to 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 such as obstructive sleep apnea, 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 caused by voluntary sleep restriction from nocturnal jobs or overwork). According to a recent inquiry from the United States, 60% of adults experience sleep problems and believe that this affects their quality of life. Another 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 billion to $100 billion in the United States [1993 National Commission on Sleep Disorders Research Executive Summary and Executive Report, National Institutes of Health, Bethesda MD 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

Because 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; Vann-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 after the administration of H₃ receptor agonists or antagonists/inverse agonists. Thiopercamide, an imidazole H₃ receptor antagonist, promoted cortical activation and waking, whereas α-methylhistamine, a chiral H₃ receptor agonist, and (R)-(−)-2-[[N-[1-(1H-imidazol-4-yl)]-2-propyl]iminophenylmethyl] phenol (BP2-94), another H₃ receptor agonist, enhanced cortical slow activity and increased slow wave sleep (Lin et al., 1990; Lin, 2000). Similar results were obtained by 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 seemed 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 with those of current wake-promoting substances such as modafinil (Bastuji and Jouvet, 1988; Lin et al., 1996a) and classic psycho-stimulants such as amphetamine and caffeine in the mouse: thiopercamide 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 1-[3-[3-(4-chlorophenyl)propoxy]propyl] piperidine, hydrochloride (BP2.649) (pitolisant), S41150, 6-[[3-cyclobuty1-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]oxy]-N-methyl-3-pyridinecarboxamide (GSK-189254), and 1-[3-[4-(piperidin-1-ylmethyl)phenoxy]propyl]piperidine (JNJ-5207852) (Barbier et al., 2004; Ligueau et al., 2007b; Zhang et al., 2007; Guo et al., 2009). Moreover, all wake-promoting agents cause a clear suppression of cortical slow waves (β and slow θ bands, mainly 0.8–5 Hz), whereas only H₃ receptor inverse agonists such as 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 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, because they may also improve vigilance and cognitive outputs. Many more recently identified compounds from different pharmaceutical companies such as BP2.649 (pitolisant), 4-(2-[[2-[[2R]-2-methylpyrrolidin-1-yl]ethyl]benzofuran-5-yl]benzonitrile (ABT-239), GSK-189254, and 4-(3-(4-piperidin-1-ylbut-1-ynyl)benzyl)morpholine (JNJ-10181457) (Fox et al., 2003, 2005; Bonaventure et al., 2007; Ligueau et al., 2007b; Medhurst et al., 2007; 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%) probably is required for wake induction rather 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; H₃ receptor antagonists are proconvulsive in children (discussed in Haas et al., 2008). Thus, H₃ receptor antagonism, through the resulting enhancement of histaminergic tone, could also be anticonvulsive.
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 seem 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 to assess whether they are mediated by the histamine neurotransmission or the H₃ receptor-regulated release of other neurotransmitters also involved in arousal, such as noradrenaline, dopamine, acetylcholine, 5-hydroxytryptamine, 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 (Parmentier et al., 2002, 2007; Toyota 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 of these results validate the hypothesis that H₃ receptor inverse agonists, through disinhibition of H₂ autoreceptors, enhance synaptic histamine release that in turn activates postsynaptic H₁ receptors and promotes waking. It is noteworthy that amphetamine and modafinil, despite their causing potent arousal, seem unlikely to depend on a histaminergic mechanism because 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 nonhistaminergic mechanisms. Whereas the wake-promoting property of H₃ receptor inverse agonists most likely depends on H₃ autoreceptor-mediated modulation of histaminergic neurotransmission, their procognitive activity seems to involve not only the histaminergic but also other neurotransmitter systems that 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 worldwide to identify clinically suitable H₃ receptor antagonists/inverse agonists. This has led to the identification of highly potent and selective compounds with good bioavailability/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 clinical trials and are being tested in sleep-wake and cognitive disorders, notably in narcolepsy: ABT-288, BF2.649 (pitolisant), GSK189254, GSK239512, JNJ-17216498, MK-0249, MK-3134, and (1R,3R)-N-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]cyclobutane-1-carboxamide (PF-03654746) (Bonaventure et al., 2007; Ligneau et al., 2007b; Medhurst et al., 2007; Medhurst et al., 2007b; Medhurst 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 worldwide. 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. It is noteworthy that modafinil amplifies the wake-promoting and antinarcopenic 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 seemed to be well tolerated by the animals because no clear signs of CNS overexcitation 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 antinarcopenic effect is seen with other H₃ receptor inverse agonists. For instance, GSK189254 suppresses narcoleptic episodes in orexin knockout mice and, unlike psychostimulants that develop toler-

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<td>BF2.649 (Pitolisant)</td>
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AD, Alzheimer’s disease; ADHD, attention-deficit hyperactivity disorder; EDS, excessive daytime sleepiness.
ance, repeated dosing reinforces selectively its antinarcoleptic effect in orexin-knockout mice (Guo et al., 2009). Furthermore, JNJ-10181457 decreases cataplexy in Doberman dogs (Bonaventure et al., 2007). After these promising preclinical data, a recent clinical trial phase II proof-of-concept study conducted in narcoleptic patients shows that pitolisant significantly improves 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.

Because 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 to prevent possible peripheral and CNS side effects such as overexcitement (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; Pas-sani et al., 2004; Ligneau et al., 2007b; 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 (Parmentier et al., 2002; Kanbayashi et al., 2009; Nishino et al., 2009). Therefore, H₃ receptor inverse agonists provide a most promising therapy for unwanted (pathological) somnolence.

Authorship Contributions

Participated in research design: Lin, Sergeeva, and Haas. Conducted experiments: Lin, Sergeeva, and Haas. Performed data analysis: Lin, Sergeeva, and Haas. Wrote or contributed to the writing of the manuscript: Lin, Sergeeva, and Haas.

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Fig. 3. Effects of pitolisant 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 pitolisant (20 mg/kg) and modafinil (64 mg/kg) enhance waking (W) and decrease slow wave sleep (SWS) and paradoxical (REM) sleep; 3) pitolisant reduces DREM episodes, whereas modafinil allows them to persist; and 4) coadministration of pitolisant and modafinil results in a greater increase in waking and a total suppression of DREM episodes (Modified from Lin et al, 2008).
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