Published in final edited form as:
Sleep Med Rev. 2011 February ; 15(1): 65–74. doi:10.1016/j.smrv.2010.06.004.

HISTAMINE IN THE REGULATION OF WAKEFULNESS

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Abstract

The histaminergic system is exclusively localized within the posterior hypothalamus with projection to almost all the major regions of the central nervous system. Strong and consistent evidence exist to suggest that histamine, acting via H_1 and/or H_3 receptor has a pivotal role in the regulation of sleep-wakefulness. Administration of histamine or H_1 receptor agonists induced wakefulness, whereas administration of H_1 receptor antagonists promoted sleep. The H_3 receptor functions as an auto-receptor and regulates the synthesis and release of histamine. Activation of H_3 receptor decreased histamine release and promoted sleep. Conversely, blockade of H_3 receptor promoted wakefulness. Histamine release in the hypothalamus and other target regions was highest during wakefulness. The histaminergic neurons displayed maximal activity during the state of vigilance, and cease their activity during NREM and REM sleep. The cerebrospinal levels of histamine were reduced in diseased states where hypersomnolence was a major symptom. The histamine deficient HDC KO mice displayed sleep fragmentation and increased REM sleep during the light period along with profound wakefulness deficit at dark onset, and in novel environment. Similar results were obtained when histamine neurons were lesioned. These studies strongly implicate the histaminergic neurons of the TMN to play a critical role in the maintenance of high vigilance state during wakefulness.

Keywords

Histamine; tuberomammillary nucleus; sleep; wakefulness; REM sleep; narcolepsy; orexins; H_1 receptor; H_3 receptor

INTRODUCTION

The state of wakefulness is an ensemble of multiple and coherent behaviors that allows the interaction with the external world. It is the manifestation of increased activity in the cortex (cortical activation or desynchronization). Increased activation of cortex is the result on concerted increase in the activity of multiple neuronal aggregates, localized in various brain regions, and utilizing multiple neurotransmitters. Each system is distinct and has a special role in the maintenance of wakefulness. For example, the glutamatergic neurons of brainstem reticular formation and the cholinergic neurons of the ponto-mesencephalic tegmentum and basal forebrain display maximal activity during wakefulness and rapid eye movement (REM) sleep and may promote cortical activation during wakefulness and REM sleep. In contrast, the monoaminergic systems namely, the norepinephrine containing locus

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coeruleus neurons, the serotonin containing neurons of the raphe nuclei and the histamine containing neurons of the tuberomammillary nucleus (TMN) are unique in the sense that these groups increase their discharge during wakefulness and completely cease firing during REM sleep. It is believed that the monoaminergic systems act in concert with other arousal systems to maintain wakefulness and inhibit REM sleep. We have focused this review on the histaminergic neurons of the TMN in the control of sleep-wakefulness. An interested reader is encouraged to consult more detailed reviews about other arousal systems and their role in sleep-wakefulness (1–5).

HISTORY OF HISTAMINE

It was in early 20th century when the sedative side effects of antihistamines were first discovered. This propelled histamine into the central nervous system (CNS) and histamine was termed as a “waking substance” (6). While research on other monoamines (norepinephrine and serotonin) in the CNS thrived during the first half of 20th century, research on histamine lagged behind, mainly because fluorescent histochemistry that revealed the presence of norepinephrinergic and serotonergic systems in the brain was unable to localize the histaminergic system in the CNS (7*), It was only after immunohistochemical studies revealed the presence of histaminergic system in the brain that histamine was awarded the coveted status of the “neurotransmitter” (8*;9*). Subsequent electrophysiological and biochemical studies demonstrated the presence of four G-protein coupled metabotropic receptors, H_1, H_2, H_3 and H_4 in the CNS (10;11).

During the last decade, availability of numerous pharmacological and molecular tools to selectively manipulate histaminergic transmission has led to significant advancement into our understanding of the functional role of histamine in the CNS. It is now believed that histaminergic neurons plays a critical role in the regulation of various behavioral and physiological functions including arousal, stress, learning and memory, pain perception, fluid balance, thermoregulation and various neuroendocrine functions. This review is focused on the role of histamine in sleep-wakefulness. However, an interested reader is encouraged to read excellent reviews on role of histamine in vertebrates and invertebrates (12–15).

ANATOMICAL LOCALIZATION OF HISTMINE NEURONS

The histamine containing neurons (Fig 1) are mainly localized in the tuberomammillary nucleus [(TMN) derived from *tuber cinerium* meaning a pale swelling; see (16*)] and adjacent areas within the posterior hypothalamus. The TMN, (the name derived from *tuber cinerium* meaning a pale swelling) was named by Malone and consists of several dense clusters of large, characteristic neurons, as well as scattered neurons with the same morphology and staining properties in surrounding, more heterogeneous regions. It is located rostral to the mammillary bodies and caudal to optic chiasm forming the floor of the third ventricle in the posterior hypothalamus (16). In all mammalian species examined, the histaminergic neurons are mainly localized within the TMN and/or surrounding regions, although minor differences do exist. For examples, in humans, the histamine containing neurons are distributed in and around the TMN (7). Although majority of histaminergic neurons in the mouse brain are localized within the TMN, the TMN is less compact and contains fewer and smaller neurons (17). In contrast, the TMN in cat brain is compact and localized mainly in the ventrolateral posterior hypothalamus (18). In guinea pigs, the histaminergic neurons are more widely distributed than in the rat and the mouse (19).

Ericson and his colleagues divided the TMN of rats into various subdivisions (20). The largest population of histaminergic neurons, termed as the ventral subgroup, was situated at the ventral surface of the brain, rostral and caudal to the mammillary bodies. The medial

subgroup was situated on each side of the mammillary recess. The diffuse part of TMN consisted of a small group of neurons scattered within the posterior hypothalamus. There is no evidence to suggest that these different subgroups have different projections. The TMN is considered as a single functional unit of histamine containing neurons, although recent studies indicate functional heterogeneity (16;21).

In addition to histamine and it synthesizing machinery, some TMN neurons also contains glutamate decarboxylase (GABA synthesizing enzyme), adenosine deaminase (enzyme involved in degradation of adenosine; only in rats but not in mice), galanin, substance P, and pro-enkephalin-derived peptides (16;22;23). The functional significance of these co-localized neuroactive substances is somewhat unclear.

The TMN neurons targets almost all major regions of the central nervous system, especially the wake-promoting basal forebrain and the orexinergic lateral hypothalamus and receives strong galanin and gamma amino butyric acid (GABA) inputs from the ventrolateral preoptic region (10;24)

SYNTHESIS AND METABOLISM OF HISTAMINE

Two distinct pools of histamine exist in the brain: neuronal and the non-neuronal pool. All brain histaminergic actions are the result of histamine released by histamine neurons in the TMN. The histamine contribution from the non-neuronal pool (mainly by mast cells) is limited (10).The blood brain barrier is impermeable to histamine. Histamine in the brain is formed from the essential amino acid L-histidine (Fig 2). Histamine synthesis occurs in two steps: 1) neuronal uptake of L-histidine by L-amino acid transporter and, 2) subsequent decarboxylation of L-histidine by a specific enzyme L-histidine decarboxylase (HDC; E.C. 4.1.1.22). The rate limiting step for histamine synthesis is the availability of L-histidine. The enzyme HDC is selective for L-histidine. Once synthesized, histamine is taken up into the vesicles by vesicular monoamine transporter and stored until released. The histamine levels in the brain are lower as compared to other monoamines, however histamine has a fast turnover (half-life <30 min) that varies significantly with the functional state. Unlike other monoamines, there is no high affinity uptake system for histamine.

Histamine, once released, is inactivated by methylation almost exclusively by the enzyme histamine-N-methyltransferase (E.C. 2.1.1.8) in the CNS. The *tele*-methyl-histamine is subsequently degraded by monoamine oxidase-B (MAO-B) and aldehyde dehydrogenase to produce *tele*-methylimidazoleacetic acid (7;18)

HISTAMINE IN SLEEP-WAKFULNESS

The first study examining the effects of antihistamines on sleep-wakefulness was performed in cats and reported increased NREM sleep coupled with reduced REM sleep (25). Similar results were also obtained in dogs and humans (26;27). Intra-ventricular (icv) application of histamine in anesthetized rat caused a dose dependent decrease in narcosis duration, whereas in conscious animals, it produced classical signs of wakefulness including EEG desynchronization, increased grooming and exploratory behavior. While pre-treatment with H_1 receptor antagonists blocked the effects of histamine, the H_2 antagonists had no effect (28–30).

In rodents, histamine synthesis, release, and degradation peaked and troughed in a circadian fashion with the highest levels observed during the dark period, when wakefulness is a predominant state and lowest during the light period when sleep is the predominant state (31;32). These initial findings suggested that histamine is responsible for the modulation of behavioral and cortical arousal via its action on histamine receptors in the brain.

Parallel research implicated the posterior hypothalamus (where the histaminergic neurons were later discovered) in the generation of arousal. It was Von Economo (1930), who first observed that lesion of the posterior hypothalamus produced sleep [cf: (33)]. Bilateral lesions in the area of the mammillary bodies induced somnolence in monkeys [Ranson, 1939, cf: (34*)]. Bilateral transections of the posterior hypothalamus reduced wakefulness in rats [Nauta, 1946, cf: (34)]. Localized and reversible inactivation by cooling the posterior hypothalamus induced behavioral sleep in rats (35). Bilateral electrolytic lesions of the posterior hypothalamus and sub-thalamic region produced a state of continuous sleep for more than one day in rats (36) and cats (37). These studies suggested that the posterior hypothalamus may contain the "wakefulness center". These findings provided the initial impetus to pursue further research to unravel the role of histamine and posterior hypothalamus in sleep-wakefulness. The next cycle of research, substantiating the role of histamine in the sleep-wakefulness consisted mainly of pharmacological, electrophysiological, and biochemical/molecular and lesion studies.

PHARMACOLOGICAL STUDIES IN ANIMALS

The bulk of evidence supporting the role of histamine in control of wakefulness was derived from pharmacological studies in animal models. For easier reading these preclinical studies are divided into subgroups and described below:

Manipulation of histamine synthesis and degradation and its effects on sleep-wakefulness

The α-fluoro-methyl-histidine (α-FMH) is an irreversible inhibitor of HDC. A single systemic injection of α-FMH (10–50 mg/kg) can produce up to 90% inhibition of HDC activity within 60–120 min resulting in marked depression of histamine levels (34).

Systemic (intraperitoneal; ip) administration of α-FMH (50 and 100 mg/Kg) resulted in decreased wakefulness and increased NREM sleep in rats and in cats (38–40). The sleep inducing effect of α-FMH began after 8 hours and lasted for 24 hr (40). Bilateral administration of α-FMH (50 μg/1 μL) into the TMN induced sleep within 2 hours. The effects lasted for 9 hours (40). Bilateral administration of α-FMH into the preoptic region of cats produced similar results (41;42).

Local TMN microinjections of SKF-91488 (50 μg/1 μL), a specific inhibitor of the catabolic enzyme histamine-N-methyltransferase, in cats immediately increased wakefulness and reduced sleep (both NREM and REM phases). The effects lasted for 6 hours (43).

These data suggests that reduction of endogenous histamine by pharmacological blockade of histamine synthesis reduced wakefulness. Conversely, increase in endogenous histamine by pharmacological blockade of histamine breakdown increased wakefulness.

Administration of histamine and its effect on sleep-wakefulness

Bilateral application of histamine into the TMN region increased arousal and latency to sleep coupled with reduction in NREM sleep in a site-specific, dose-dependent manner in cats. The highest dose (60 pg) produced maximal increase in wakefulness that lasted for 6 hours suggesting that histamine is a potent wakefulness promoting agent. Pretreatment with the histamine H_1 receptor antagonist mepyramine completely blocked arousal inducing effects of histamine suggesting that the histamine mediates it wakefulness promoting effect via H_1 receptors (40;43). Similar effects were observed when histamine was bilaterally administered into the pontine tegmentum or preoptic region of cats. Pretreatment with H_1 receptor antagonist mepyramine attenuated arousal inducing effects of histamine (41;42).

Repeated low frequency stimulation of the midbrain reticular formation increased cortical EEG spectral power in low frequency bands (0–6 Hz). This effect was blocked by central (icv) administration of histamine and reversed by simultaneous administration of H_1 receptors antagonist, but not H_2 receptors antagonist (44;45).

Bilateral reverse microdialysis administration of histamine into the cholinergic basal forebrain of rats produced a site specific, dose-dependent increase in wakefulness with a concomitant decrease in NREM sleep without affecting REM sleep implicating that histamine induced wakefulness may be mediated via the cholinergic basal forebrain (46).

Administration of H_1 receptor agonists/antagonist and its effect on sleep-wakefulness

The H_1 receptor is a typical G protein-coupled metabotropic receptor (~490 amino acids) with seven putative transmembrane domains (47). Encoded from the intronless region on human chromosome 3, the H_1 receptor is coupled to phospholipase C through a pertussis toxin-insensitive ($G_{q/11}$) G protein (48). The H_1 receptor is widely distributed throughout the brain with high to moderate levels found in sleep-wakefulness regulatory regions including the basal forebrain, locus coeruleus, raphe nuclei, mesopontine tegmentum and the thalamus (49).

Systemic (ip) administration of the first generation H_1 receptor antagonists pyrilamine and diphenhydramine decreased W and increased NREM sleep in rats. Central administration of the H_1-receptor agonist 2-thiazolylethylamine, dose-dependently, increased wakefulness and decreased both NREM and REM sleep. Furthermore, the H_1 receptor antagonists pyrilamine blocked the wakefulness inducing effects of 2-thiazolylethylamine (50).

Bilateral administration of 2-thiazolylethylamine (50 μg/0.5 μL) into the pontine tegmentum of cats increased wakefulness and reduced NREM sleep during the first 3 hr post-injection. Conversely, bilateral application of mepyramine (5 μg/0.25 μL) into the pontine tegmentum of cats reduced wakefulness and increased NREM sleep suggesting that histamine may mediate wakefulness via activation of H_1 receptors in wakefulness regulatory mesopontine tegmentum (42). Systemic injections of H_1 receptor antagonist mepyramine (1 and 5 mg/Kg) dose-dependently increased NREM sleep and decreased wakefulness, REM sleep and latency to sleep within 1 hour after injections. However, local application of mepyramine (120 μg/μL) into the TMN reduced wakefulness and increased sleep (both NREM and REM phases) without affecting NREM sleep latency (40).

Systemic administration of H_1-antagonists, promethazine, diphenhydramine, or chlorpheniramine had no effect on sleep-wakefulness in rats housed on sawdust. However, rats housed on grid above water displayed increased NREM sleep suggesting that the H_1-antagonists had potent sedative effects only when the histaminergic system is activated (51).

Administration of H_2 receptor agonists/antagonist and its effects on sleep-wakefulness

The H_2 receptor is coupled to adenylyl cyclase via the GTP-binding G_s protein. Activation of H_2 receptor causes an accumulation of cAMP and activation of protein kinase A (52). Medium to low densities of H_2 receptor are observed in sleep-wakefulness regulatory centers including the thalamus, basal forebrain, posterior hypothalamus, locus coeruleus, raphe nuclei and TMN (53). However, central or systemic administration of H_2-receptor agonists and/or antagonists had no effect on sleep-wakefulness in rats (50;54). Similar results were obtained after local application of H_2 receptor agonist, impromidine (0.2μg/0.25 μL), in the pontine tegmentum. However, application of impromidine (1 μg/1 μL), into the preoptic region of the cat induced wakefulness (41;42).

Administration of H3 receptor agonists/antagonist and its effects on sleep-wakefulness

Identified first in 1983, the H_3 receptor functions as an auto-receptor and regulates histamine release (55). Coupled to pertussis toxin sensitive $G_{i/o}$ protein, the H_3 receptor has high constitutive signaling activity *in vivo, a* unique characteristic that is rarely observed *in vivo* (56;57).

Oral administration of thioperamide, an H_3 receptor antagonist, produced a dose dependent and protracted wakefulness. The highest dose (10 mg/Kg) produced maximal increase (>50 %) in wakefulness that lasted for 10 hours. The arousal effects of thioperamide were prevented by pretreatment with (R) α-methyl-histamine (H_3 agonist; 20 mg/kg) or mepyramine (1mg/Kg). Conversely, oral administration of (R) α-methyl-histamine to cats enhanced NREM sleep in a dose dependent manner. The highest dose of (R) α-methyl-histamine (20 mg/Kg) increased NREM sleep (>50%) that lasted for 6 hr (58). These were among the first studies to demonstrate the role of H_3 receptors in the regulation of wakefulness.

While systemic administration of thioperamide increased wakefulness and reduced sleep in a dose dependent fashion, systemic administration of (R) α-methyl-histamine had no effect on sleep in rats. In contrast, bilateral application of (R) α-methyl-histamine into the TMN region increased NREM sleep with a concomitant decrease in wakefulness and REM sleep suggesting that activation of H_3 receptor in the TMN is likely to block histamine release resulting in reduced wakefulness. The NREM inducing effect of (R) α-methyl-histamine was attenuated if the rats were pretreated with thioperamide (59).

Oral administration of BP 2.94 (20–30 mg/Kg) produced a dose dependent increase in NREM sleep without affecting wakefulness or REM sleep in rats. Pretreatment with H_3 receptor antagonist carboperamide (30 mg/Kg) prevented the sleep inducing effects of BP 2.94 in rats. Conversely, oral administration of carboperamide (20–30 mg/Kg) produced a dose dependent increase in wakefulness with a concomitant decrease in NREM and REM sleep (60). Similarly, oral administration of H_3 receptor agonist BP 2.94 induced a dramatic increase in NREM sleep in cats (61*).

Oral administration (10 mg/kg) of H_3 receptor agonist, Sch 50971, depressed locomotor activity and increased total sleep time in guinea pigs (62). In contrast, oral administration of ciproxifan (0.15–2 mg/kg), a H_3 receptor antagonist, induced wakefulness in cats (63). However, ip injections of immepip (5 or 10 mg/kg; H_3 receptor agonist) in rats did not produce major changes in sleep, although cortical histamine release was significantly reduced (64).

Systemic (subcutaneous; sc) administration of thioperamide (10 mg/kg), in H_3 receptor (−/−) knockout (H_3R-KO) mice had no effect on sleep. However, increased wakefulness coupled with decreased NREM sleep was observed during the first 2 h after administration (at lights-on) in wild type mice. REM sleep remained unaffected (65).

Systemic injections (1–10 mg/Kg; sc) of a highly selective and a novel non-imidazole H_3 receptor antagonist, 1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperidine (JNJ-5207852) increased wakefulness with a concomitant decrease in sleep (both NREM and REM phases) coupled with reduced total delta power in mice and rats (66).

Vanni-Mercier and his colleagues (67) investigated the effects of H_3 receptor ligands on the discharge activity of TMN neurons in freely behaving cats. Systemic (intramuscular; im) injection of ciproxifan (1 mg/kg) increased wakefulness and rapidly (> 15 min) increased the activity of wake-active TMN neurons for 2 hours. Local TMN application of (*R*)-α-methyl-

histamine blocked the effects of ciproxifan. Conversely, systemic injection of the H_3 receptor agonist imetit (*S*-[2-4-(imidazolyl)ethyl]isothiourea), a (1 mg/kg, i.m.), reduced the activity of wake-active TMN neurons for 3 hour. Behaviorally the animals appeared drowsy and the EEG displayed increased slow wave and spindles. The effects of imetit were reversed by systemic injection of ciproxifan. Local administration of (*R*)-α-methyl-histamine into the TMN, dose dependently, decreased the activity of wake-active TMN neurons without affecting behavioral states. The highest dose (0.1 μg/0.2 μl) ceased the activity completely within 30 min post-injection (67).

Acute oral administration of GSK189254 (H_3 receptor antagonist; 3 and 10 mg/kg) increased wakefulness and reduced sleep (NREM and REM phases) in wild type (orexin +/+) and orexin KO mice and reduced episodes of narcolepsy (sleep onset REM sleep) in orexin KO mice. However, after chronic administration of GSK189254 (10 mg/kg; twice daily for 8 days), the effect on wakefulness was significantly reduced in both wild types and orexin KO. In addition, significant increase in narcoleptic episodes was observed in orexin KO (68).

In another study, oral administration of tiprolisant (H_3 antagonist; 20 mg/kg) in orexin KO, at dark onset, promoted wakefulness coupled with increased theta and gamma activity in the EEG and reduced episodes of narcolepsy (sleep onset REM sleep). However, there was no significant difference in cortical levels of *tele*-methyl histamine (histamine metabolite) between wild type (orexin (+/+) and orexin KO suggesting that histamine levels were not altered. Interestingly, co-administration of modafinil [currently used drug for the treatment of excessive daytime sleepiness in narcolepsy; 64g/kg; orally] with tiprolisant (orally, 20 mg/Kg) was strongly enhanced the effects of tiprolisant (69).

As described above, strong pharmacological evidence exists to suggest that administration of H_3 receptor antagonist produced strong wakefulness. Interestingly, acute administration of H_3 receptor antagonist reduced narcoleptic episodes and increased wakefulness, however, repeated dosing of H_3 antagonist resulted in increased narcoleptic episodes coupled with reduced effects on wakefulness.

PHARMACOLOGICAL STUDIES IN HUMANS

As described above, the first generation anti-histamine can easily penetrate the blood brain barrier and cause drowsiness and sedation. Several of these anti-histamines including the non-selective H_I receptor antagonists from the phenothiazine class and “over the counter” diphenhydramine, have been examined for their effects on daytime sleepiness as well as on subjective and objectives measures of nocturnal sleep in healthy human subjects sleep and are extensively reviewed elsewhere (70;71). We have sampled some studies and presented here.

Administration of promethazine at bed time, in healthy volunteers, induced a dose dependent reduction in REM sleep followed by a significant increase in REM sleep (REM rebound) on post-drug “withdrawal” night. Significant increases in Stage 2 NREM sleep (50 and 100 mg) and Stage III and IV (200 mg) were also observed (26). In the second part of the same study, administration of promethazine for 9 days (100 mg at bed time) induced a profound suppression of REM sleep that peaked on day 1 and returned to placebo values by day 9, followed by REM rebound on post-drug withdrawal day 10 (26). In contrast, Adam and Oswald (1986) reported increased stage II NREM after 20 and 40 mg dose of promethazine. Reduction in REM sleep was observed only with the 40 mg dose (72). Self assessment of sleep quality and sleep latency improvements substantiated by significant reduction in latency to NREM sleep (stage 1) was observed after bedtime administration of propiomazine (25 mg) for 5 days (73).

A single bed time dose (50 or 75 mg) of “over the counter”, antihistamine diphenhydramine, increased motor activity without affecting any subjective sleep parameter (74). Significant improvement in subjective sleep parameters were also observed after diphenhydramine (50 mg) administration in moderately insomniac (75).

The recent development of non-imidazole H_3 receptor ligands with reduced risk of drug-drug interaction has provided many potential clinical candidates that can be used to correct sleep-wakefulness disorders including narcolepsy (76–78). In a recent sequential placebo-controlled, single-blind study, 21 narcoleptic patients were administered a fixed dose of 40 mg tiprolisant (H_3 receptor antagonist) for 7 days and excessive daytime sleepiness (EDS) was examined by the subjective Epworth sleepiness scale. Significant improvements in EDS were observed with tiprolisant as compared to placebo (79). This study was among the first to demonstrate therapeutic relevance of H_3 receptor antagonist as potential clinical candidates for the treatment of narcolepsy. Besides tiprolisant, many other H_3 receptor antagonists including JNJ-17216498, GSK189254, BF2.649, APD916, and PF-03654746 are under investigation for the treatment of various sleep-wakefulness disorders including narcolepsy (76;78;80).

ELECTROPHYSIOLOGICAL STUDIES

IN VITRO STUDIES

The TMN neurons—The histamine containing TMN neurons are spontaneously active at resting potential (−50 mV) with broad shouldered spike (mid-amplitude duration ~2 ms), mainly due to fast Na+ and Ca+ conductions and a deep (~15 mV) and long lasting Ca+ independent after-hyperpolarization (~450 ms duration) that brings the membrane potential down to −80 mV (81). The onset of an action potential is the result of slow depolarizing potential mediated by voltage dependent Ca^{2+} current and a slow tetrodotoxin (TTX) sensitive Na+ current. The Ca^{2+} current is activated by a return to threshold following after-hyperpolarization, whereas the Na^+ current appears to be persistent (82). The action potential is followed by after-hyperpolarization which is responsible for limiting the discharge activity. A fast transient K^+ outward current (A-type) with two components may be critical for membrane re-polarization, and together with a hyperpolarization -activated current (I_h), it provides a strong inward- and outward rectifications similar to other monoaminergic neurons (10).

Post synaptic effects of histamine on other sleep-wakefulness regulatory sites Dorsal Raphe—Although, H_2 receptor mediated depression of dorsal raphe firing has been reported (83), histamine activates the dorsal raphe neurons via H_1 receptor mediated opening of a mixed cation channel of the transient receptor potential cation channel family (84;85).

Locus coeruleus—Majority of norepinephrine containing locus coeruleus neurons are excited by histamine via H_1 receptor. The H_2 receptor mediated excitation of norepinephrine containing locus coeruleus neurons has been observed. However, the H_3 receptor mediated electrophysiological actions have not been reported (86).

Basal forebrain and the brainstem cholinergic neurons—The cholinergic neurons of the mesopontine tegmentum and basal forebrain are excited by histamine, mediated via the activation of H_1 receptor (87;88). Activation of H_3 receptor results in the depression of cholinergic neurons coupled with reduction in cortical acetylcholine release (89;90).

Ventrolateral and medial preoptic neurons—*In vitro* studies suggest that histamine does not have any effect on sleep-active neurons of the ventrolateral preoptic region (91).

However, activation of H_1 receptor causes excitation of GABA neurons in the medial preoptic region (92;93).

Perifornical lateral hypothalamus—*In vitro* studies suggest that histamine has no direct effect on orexinergic neurons of the perifornical lateral hypothalamus, although strong anatomical connection are present (24;94)

Thalamus—Histamine promotes depolarization of thalamic relay neurons via combined activation of H_1 and H_2 receptors (95).

IN VIVO STUDIES

Early studies examined extracellular single unit activity of presumed histaminergic neurons from the TMN in urethane-anesthetized and conscious rats, and conscious cats. These studies suggested that presumed histaminergic neurons displayed discharge pattern that was similar to other monoaminergic neurons; slow tonic discharge during wakefulness, reduced discharge during NREM sleep, complete cessation during REM sleep and resumption of firing in anticipation of wakefulness. These REM-off neurons displayed long duration action potentials and slow conduction velocity suggesting unmyelinated histaminergic axons (96–99)

Recently, extracellular activity was examined from identified histaminergic neurons from the TMN of non-anesthetized, head-restrained mice (100*). The histaminergic neurons displayed broad triphasic action potentials with a slow (<10 Hz) tonic, and repetitive firing pattern that strongly correlated with state of vigilance. The maximal activity was observed during attentive wakefulness that dramatically reduced during quite wakefulness. Complete cessation of activity was observed during the state of drowsiness, NREM and REM sleep state. A pronounced delay in the discharge activity was observed during the transition from sleep to wakefulness. The histaminergic neurons resumed their activity only after the animal was fully alert. Based on these results, the authors concluded that histamine neurons may play a pivotal role in the maintenance of an arousal state of high vigilance that is required for cognitive processes. Conversely, cessation of histaminergic activity may play a role in initiation and maintenance of sleep (100).

BIOCHEMICAL/MOLECULAR STUDIES

Measurement of histamine release and turnover

The histaminergic system appears to be under strong circadian control. Microdialysis measurement of histamine release from the anterior hypothalamic area of freely behaving rats, maintained under 12:12 h light:dark cycle, revealed that histamine release anticipated wakefulness and increased during the second half of the light period. The histamine release peaked during the dark period when the rats were fully awake and active (101). Similar results were obtained after push-pull cannula measurement of histamine release from the posterior hypothalamus in freely moving rats (102). Diurnal variations in the levels of histamine metabolites (tele-methylhistamine and tele-methylimidazoleacetic acid), with the peaks during active period (daytime) and troughs during inactive period, were observed in the cerebrospinal fluid (CSF) of rhesus monkey (103). Diurnal variations in CSF levels of telemethylhistamine (histamine metabolite) in human children has also been reported (104).

Microdialysis measurements of histamine, from pre-optic/anterior hypothalamus, across behavioral states in freely behaving cats suggested that histamine levels peaked during wakefulness and troughed during REM sleep (Fig.3). Interestingly, histamine levels did not increase during sleep deprivation suggesting that the histamine levels do not convey the

"sleep drive" information to the sleep-promoting neurons of the preoptic hypothalamus (105).

Measurement of c-Fos immunoreactivity as a marker of neuronal activation

Since its discovery in the 1980s, expression of immediate-early gene *c-fos*, and the subsequent accumulation of c-Fos protein has often been used as a maker of neuronal activation (106). This characteristic of c-Fos protein has been extensively used, in sleep research, to identify the neurochemical phenotype of activated neurons across sleep-wakefulness (107)

Systemic administration of a H_3 receptor antagonist, ciproxifan (1 mg/kg in 0.2 ml, i.m), induced c-Fos expression in vast majority of histaminergic neurons in the TMN (67). Systemic administration of anesthetic agent pentobarbital (100 mg/Kg) and propofol (140 mg/Kg), $GABA_A$ receptor agonist muscimol (10 mg/Kg), and α_2 receptor agonist dexmedetomidin (500 μg/Kg) produced significant reduction in c-Fos protein in the TMN (108;109). Infusion of prostaglandin D_2 (200 pmol/min) or adenosine A_{2a} receptor agonist CGS21680 (20 pmol/min) into the subarachnoid space, during the dark period, increased NREM sleep and reduced c-Fos expression in the TMN of rats. In contrast, infusion of adenosine A_1 receptor agonist N6-cyclopentyl-adenosine (2 pmol/min) in the same area did not have any effect on sleep-wakefulness or c-Fos expression in the TMN (110;111).

Rats maintained in free running condition (constant darkness) display increased wakefulness and c-Fos protein in the TMN during the subjective night irrespective of the lighting condition suggesting a strong co-relationship between c-Fos expression in the TMN and the amount of wakefulness independent of circadian cycle (112).

Measurement of sleep-wakefulness in knockout mice

Sleep-wakefulness in H_1 receptor (−/−) KO—The H_1 receptor KO (H_1R-KO) displayed essentially normal sleep-wakefulness under normal baseline conditions (113). Minor deficits including loss of brief awakenings (<16 sec bouts) and increased NREM sleep duration were observed in H_1R-KO as compared to wild type mice. Systemic injection of ciproxifan induced wakefulness in wild type mice. No such effect was observed in H_1R-KO validating the loss of H_1 receptor knockdown. However, ciproxifan induced histamine release in the frontal cortex was identical in both wild type and H_1R-KO mice suggesting that the histamine release in not controlled by H_1 receptor (113).

Sleep-wakefulness in H_3R- KO—Similar to H_1R-KO, the H_3 receptor KO (−/−; H_3R-KO) mice display essentially normal sleep-wakefulness under baseline condition with a small reduction in locomotor activity during the dark period (114). However, as described above, systemic administration of thioperamide was ineffective in H_3R-KO, but increased wakefulness in wild type mice (H_3 +/+) mice suggesting that the H_3 receptors have an important role in mediating behavioral arousal (114).

Sleep-wakefulness in HDC (−/−) KO and it comparison with orexin KO—The recently discovered orexin neurons are exclusively localized in the perifornical hypothalamus, in close proximity to the histaminergic neurons, and like the histaminergic neurons send widespread projections to the entire brain including those involved in the regulation of sleep wakefulness. Like the histaminergic neurons, the orexin neurons are wake-active, reduce their activity during quite wakefulness and are completely silent during NREM and REM sleep. In addition, orexin neurons send strong projections to the histaminergic neurons and orexin receptors are localized on histaminergic neurons. A large body of evidence indicates that deficiency in orexins is the cause for the pathogenesis of

human and animal narcolepsy (115–117). Reduced histamine has been observed in CSF of narcoleptics (discussed below). These similarities between orexins and histamine raised questions: Do orexin and histamine containing neurons have similar or distinct role in control of wakefulness? Are these two systems co-responsible for narcolepsy? Anaclet et al., (2009) compared the behavioral and sleep-wakefulness phenotypes of HDC (−/−) KO mice with those of orexin (prepro-orexin −/−) KO mice. The HDC KO mice displayed histamine deficiency due to complete absence of histamine synthesis (17;118). The orexin KO displayed orexin deficiency. Both orexin and HDC KO mice displayed sleep fragmentation and increased REM sleep. However, there were several major differences: 1) The HDC KO displayed increased REM sleep during the light (inactive) period; the orexin KO displayed increased REM sleep during the dark (active) period. 2) The HDC KO displayed wakefulness deficit at dark onset and in novel environment; the orexin KO do not. 3) The orexin KO displayed impaired circadian distribution for both wakefulness and REM sleep; the HDC KO do not. 4) When faced with a motor challenge, the orexin KO displayed narcolepsy; the HDC KO do not. Based on these results, the authors concluded that the orexins and histamine neurons exert a distinct, but complementary and synergistic control in wakefulness maintenance (119*).

Role of orexins in the histaminergic TMN

Local reverse microdialysis administration of orexin A (5 and 25 pmol/min) into the TMN of rats increased histamine release and wakefulness with a concomitant reduction in sleep (both NREM and REM phases). Furthermore, central infusion of orexin A (1.5 pmol/min) increased wakefulness in wild-type mice, but not in H_1 receptor (−/−) KO mice suggesting that the arousal effect of orexins are dependent on the activation of H_1 receptor in the TMN (120).

Role of adenosine in the histaminergic TMN

A distinctive feature of many (but not all) histaminergic neurons in the TMN of rats (not the mouse) is the presence of high levels of adenosine deaminase, a key enzyme involved in deamination of adenosine (7). Adenosine is a mediator of homeostatic sleep regulation (121;122). Recently, it has been demonstrated that adenosine A_1 receptors are expressed on histaminergic neurons of the TMN. Activation of A_1R or inhibiton of adenosine deaminase in the TMN decreased histamine release in the frontal cortex and increased non-rapid eye movement (NREM) sleep without affecting rapid eye movement (REM) sleep. Activation of A_1 promoted sleep in wild type mice, but not in A_1 receptor or H_1 receptor knockout mice (123).

INACTIVATION/LESION STUDIES

Inactivation of the ventro-lateral posterior hypothalamus (in and around the TMN) by local application of muscimol (0.1–1.0 μg/0.5 μL), a potent agonist of GABA, induced long-lasting NREM sleep followed by a significant increase in REM sleep. Systemic administration of p-chlorophenylalanine, a potent serotonin synthesis inhibitor produces long lasting insomnia. Local administration of muscimol in these insomniac cats induced NREM and REM sleep with short latency (124)

Local administration of the neurotoxin saporin conjugated to orexin B (hypocretin 2, 50 ng in 0.25 μL) into the TMN, destroyed up to 83% of histaminergic neurons along with other neurons in the TMN. The sleep-wakefulness remained unaffected. However, compensatory effects following lesion cannot be ruled out because the neurons take several days to die following the administration of the neurotoxin (125).

In a subsequent study, sleep-wakefulness was examined following simultaneous lesions of three wake-promoting neuronal groups with three different saporin-conjugated neurotoxins. The basal forebrain cholinergic neurons were lesioned by 192-IgG-saporin (6 μg/3μ; icv). The noradrenergic neurons were lesioned by bilateral locus coeruleus injections of anti-dopamine-β-hydroxylase-saporin (0.25 μg/0.25 μL/side), and the histaminergic neurons were lesioned by bilateral and injections of orexin B-saporin conjugate (62.5 ng/0.25 μL/side) into the TMN. Simultaneous lesion of three wakefulness-promoting regions did not affect sleep-wakefulness, except that rats with triple lesions displayed wakefulness deficit at dark onset. It is important to note that wakefulness deficit at dark onset is also observed in HDC-KO. Thus, these data clearly suggest that the histamine neurons may have a major role in the maintenance of the wakefulness state (126).

HISTMINE IN DISEASED STATES

The monoaminergic LC and 5-HT neurons reduced or ceased their activity during cataplexy in narcoleptic dogs. However, the histaminergic neurons of the TMN remained active (127). Narcoleptic dogs displayed histamine deficit in the cortex and thalamus. In contrast, dopamine and NE levels were elevated in the same brain structures (128). Similarly, CSF levels of histamine were reduced in non-medicated human subjects with narcolepsy or idiopathic hypersomnia. However, similar reduction was not observed in human subjects with obstructive sleep apnea (*129;130). The authors concluded that CSF histamine can be used as a biomarker reflecting the degree of hypersomnia of central origin (129). While these finding are interesting and novel, they were some limitations. For example, considerable overlap in histamine values was observed between controls and patients. In addition, substantial variability of histamine levels was observed within groups (131).

CONCLUSION

Does histaminergic system regulate wakefulness? The histaminergic system is localized within the TMN, which is a nucleus in the posterior hypothalamus. Since the early part of the 20th century, posterior hypothalamus has been implicated in the regulation of wakefulness. The histaminergic neurons send strong projections especially to the wakefulness promoting regions including the orexin rich perifornical hypothalamus and the cholinergic rich basal forebrain. The discharge activity of identified histaminergic neurons peaked during the state of high vigilance and ceased during NREM and REM sleep. Histamine release parallels histaminergic discharge, highest during wakefulness and lowest during sleep. Considerable pharmacological evidence suggests that the H_1 and H_3 receptor (but not the H_2 receptors) are key mediators of histaminergic action on wakefulness. The HDC KO displayed wakefulness deficit at dark onset and in novel environment. Thus, there is plethora of evidence implicating histaminergic system to play a crucial role in the regulation of wakefulness. The challenges for the future are: 1) to identify the precise, cellular and the molecular mechanisms by which histamine acts to maintain the high state of vigilance, 2) to examine whether histamine or one of its metabolites can be used to diagnostic tool in diseased states and 3) to create selective and specific histamine H_3 receptor ligands that can be used to treat sleep-disorders.

PRACTICE POINTS

1. The histaminergic neurons in the brain are exclusively localized in the tuberomammillary nucleus in the posterior hypothalamus.

2 The histaminergic neurons display increased discharge activity during the state of high vigilance and are completely silent during states of drowsiness, NREM and REM sleep.

3 Mice with constitutive deletion of L-histidine decarboxylase gene display histamine deficit coupled with sleep-wake disruptions.

RESEARCH AGENDA

4 To explore the possibility of using CSF histamine or one of its metabolites as biomarkers in diseases state with hypersomnolence of central origin.

5 To develop novel and selective histamine H_3 receptor ligands that can be used to treat sleep disorders including narcolepsy.

6 To further understand the role of histamine in cognition and novelty induced arousal.

ABBREVIATIONS

α-FMH	α-fluoro-methyl-histidine
CSF	cerebrospinal fluid
GABA	Gama amino butyric acid.
HDC	L-histidine decarboxylase.
H_1R-KO	Histamine H_1 receptor knockout
H_3R-KO	Histamine H_3 receptor knockout
icv	intraventricular
ip	intraperitoneal
im	intramuscular
KO	constitutive knockout mice
NREM	non-rapid eye movement sleep
REM	Rapid Eye Movement
sc	subcutaneous
TMN	Tuberomammillary nucleus

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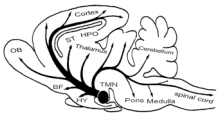

Figure 1.

Schematic representation of the location and distribution of the histaminergic system in the brain. The histamine containing neurons are localized in the tuberomammillary nucleus (TMN) within the posterior hypothalamus and send projections throughout the brain. Abbreviations: BF = basal forebrain; HPO= hippocampus; HY = hypothalamus; OB = Olfactory bulb; ST= Striatum; TMN = tuberomammillary nucleus; Adapted from (118).

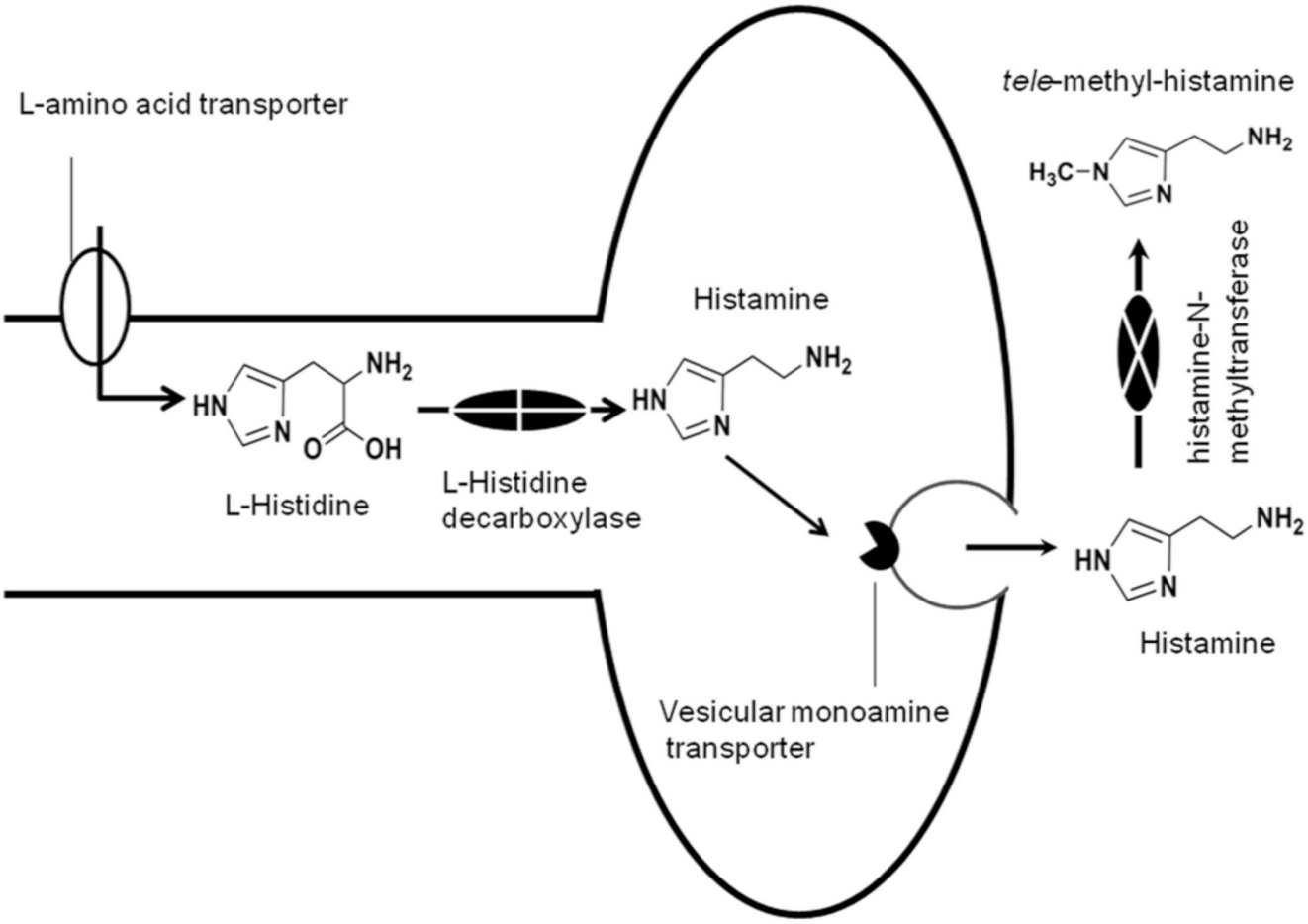

Figure 2.

Histamine synthesis and metabolism in neurons. The L-histidine is transported into neurons by L-amino acid transporter. Once inside the neuron, L-histidine is converted into histamine by a specific enzyme histidine decarboxylase. Subsequently histamine is taken up into vesicles by the vesicular monoamine-transporter and stored until released. In absence of high affinity uptake mechanism in the brain, released histamine is quickly degraded by histamine methyltransferase which is located post-synaptically and in glia to tele-methyl-histamine, a metabolite that does not show any histamine-like activity.

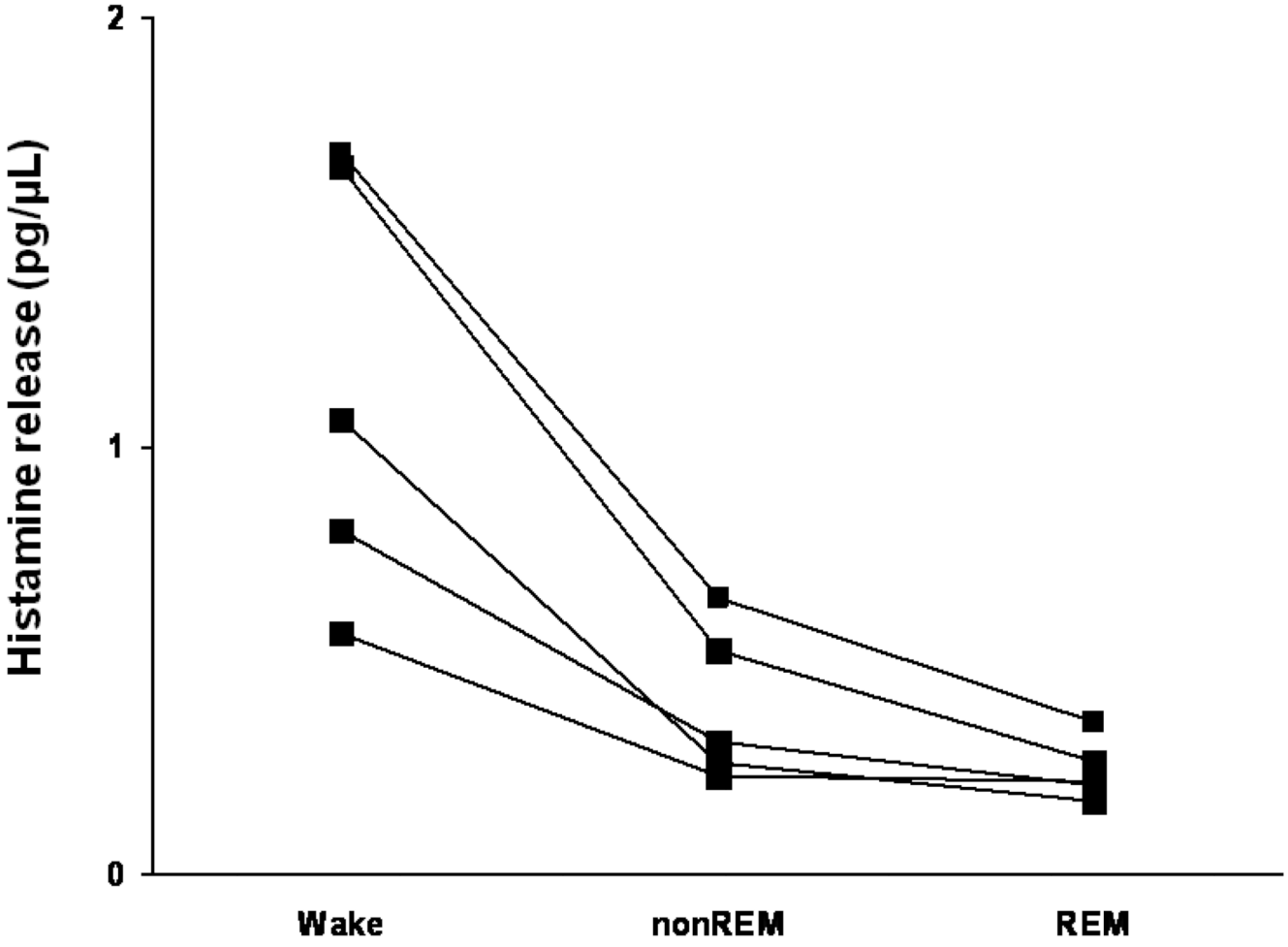

Figure 3.
Histamine release measured from the preoptic/anterior hypothalamus of freely behaving cats across sleep-wakefulness. Histamine release was higher during wakefulness as compared non-REM and REM sleep values in each experiment (represent by each line) producing a highly significant group effect [N=5; for details see (105); Adapted from (105).