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Review

Acetylcholine, Histamine, and Cognition: Two Sides of the Same Coin

Patrizio Blandina,[1] Marcel Efoudebe, Gabriele Cenni, Pierfrancesco Mannaioni, and Maria Beatrice Passani

Dipartimento di Farmacologia Preclinica e Clinica, V.le G. Pieraccini 6, Universitá di Firenze, 50139 Firenze, Italy

The forebrain cholinergic neurons are localized in the nucleus basalis magnocellularis (NBM), the major source of cholinergic innervation to the neocortex and to the amygdala, and in the medium septum-banda diagonalis complex, which provides cholinergic inputs to the hippocampus (Mesulam et al. 1983; Woolf et al. 1984; Nicoll 1985). Basic and clinical studies have linked dysfunctions of these neurons to cognitive decline (Everitt and Robbins 1997; Givens and Sarter 1997). Their extensive loss is characteristic of the forebrain of Alzheimer's disease patients (Davies and Maloney 1976; Coyle et al. 1983; Kuhl et al. 1999), and anticholinergic drugs, such as scopolamine and atropine, produce learning and memory deficits in a variety of cognitive animal models (Deutsch 1971; Bartus and Johnson 1976; Ennaceur and Meliani 1992), and affect recognition memory in humans (Sperling et al. 2002; Sherman et al. 2003). Moreover, aged rodents display both cognitive impairments in many learning tasks (Ingram et al. 1994) and cholinergic deficits (Kubanis and Zornetzer 1981; Decker 1987; Gallagher and Colombo 1995). However, neuronal alterations associated with cognitive deficits are not restricted to the cholinergic systems. For instance, dysfunctions of dopamine, GABA, noradrenaline, serotonin, and histamine neurons have been identified in Alzheimer's disease (Hardy et al. 1985; Airaksinen et al. 1991; Panula et al. 1997; Schneider et al. 1997), and region-selective decreases in dopaminergic, noradrenergic, or serotonergic contents are associated with the level of age-related learning and memory impairments (Stemmelin et al. 2000; Birthelmer et al. 2003). Abnormal interactions between malfunctioning cholinergic and other neurotransmitter systems may cause additive or even synergistic effects on cognition, a phenomenon that warrants the increasing interest in understanding the complex physiology of brain systems affecting cognitive processes. In this regard, the role of histamine is gaining increasing attention (Passani et al. 2000; Passani and Blandina 2003), and many recent results indicate that the histaminergic system influences learning and memory by modulating the release of ACh (Passani et al. 2000; Bacciottini et al. 2001), although some cognitive effects of histamine and histaminergic agents occur independently of ACh. For example, local administration of histamine failed to affect ACh release from the hippocampus (Bacciottini et al. 2002), yet improved fear memory by H2- or H3-receptor-elicited erk2 activation in hippocampal CA3 cells (Giovannini et al. 2003). Nevertheless, histaminergic efferents influence both the NBM-cortical (Clapham and Kilpatrick 1992; Blandina et al. 1996; Cecchi et al. 2001) and the medium septum-banda diagonalis-hippocampal cholinergic pathways (Mochizuki et al. 1994; Bacciottini et al. 2002; Fig. 1). The regulation of ACh tone in different brain areas by neuronal histamine also encompasses functions other than cognition. Histamine promotes wakefulness by tonic control over sleep-generating mechanisms in the preoptic/anterior hypothalamus, and cholinergic neurons seem to be implicated (Lin et al. 1994; Brown et al. 2001). The aim of this review is to summarize some of the most recent work on the interactions between histaminergic and cholinergic systems, and evaluate their role in cognitive and other brain functions.

[1]**Corresponding author.**
E-MAIL patrizio.blandina@unifi.it; FAX 39-0554271280.
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Histamine in the Central Nervous System

Histaminergic cell bodies are located exclusively in the tuberomammillary nucleus of the hypothalamus (Watanabe et al. 1983; Panula et al. 1984), which is also the sole location of histidine decarboxylase immunoreactivity (Ericson et al. 1987), an essential determinant of brain histamine levels (Kollonitsch et al. 1978; Green et al. 1987). These neurons project efferent varicose fibers to all areas of the central nervous system (Inagaki et al. 1990). Histaminergic fibers are mostly unmyelinated and make relatively few synaptic contacts, mainly with dendritic shafts (Tohyama et al. 1991), with the exception of the mesencephalic trigeminal nucleus, in which numerous synaptic contacts have been observed by electron microscopy (Inagaki et al. 1987). Histamine interacts with specific receptors; three metabotropic, histaminergic receptor subtypes, H1, H2, and H3 have been described in the mammalian central nervous system (Hill et al. 1997). Expression of a fourth histaminergic receptor was shown in the peripheral tissue (Oda et al. 2000), but its presence in the brain is still controversial (Liu et al. 2001a,b; Zhu et al. 2001). All histaminergic receptors show a high degree of agonist-independent activity. This phenomenon is referred to as constitutive activity, and occurs in human, rat, and mouse recombinant receptors expressed at physiological concentrations (Smit et al. 1996; Bakker et al. 2000; Morisset et al. 2000; Wieland et al. 2001). It has been suggested that constitutive activity of native H_3 receptors is one of the highest among G-protein-coupled receptors in the brain (Rouleau et al. 2002). Constitutively active H_3 receptors presumably regulate histaminergic neurons, hence, the release of histamine (Morisset et al. 2000). In this respect, the reclassification of those H_3 receptor antagonists such as clobenpropit, thioperamide, and ciproxifan that block constitutive activity, as inverse agonists, may have therapeutic relevance. Either inverse agonists or neutral antagonists may be favorable for different clinical applications. Some histaminergic neurons also store neuroactive substances and related enzymes, such as GABA (Ericson 1991), glutamate decarboxylase (Takeda et al. 1984), adenosine deaminase (Senba et al. 1985), substance P (Köhler et al. 1985) and galanin (Köhler et al. 1986), in a species-specific manner (Airaksinen 1992), but the functional significance of these colo-

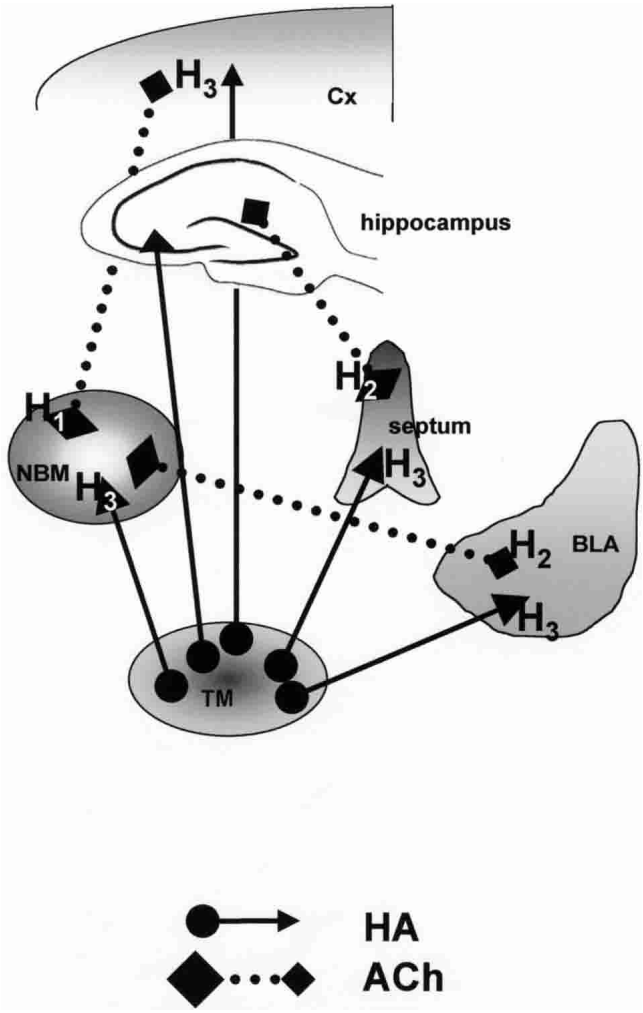

Figure 1 Schematic representation of the interactions between the cholinergic and histaminergic systems in some regions of the rat brain. The location of histaminergic receptors is inferred from results obtained using the microdialysis technique (see text). (BLA) basolateral amygdala; (Cx) cortex; (NBM) nucleus basalis magnocellularis; (TM) tuberomammillary nucleus.

calizations is unknown at the moment. The morphological features of the central histaminergic system, with a compact cell group and a widespread distribution of varicose fibers, resembles that of other biogenic amines, such as norepinephrine and serotonin, thus suggesting that the histaminergic system may also act as a regulatory center for whole-brain activity (Wada et al. 1991). Histaminergic neurons fire spontaneously (Reiner 1987; Haas and Reiner 1988) at a low rate during sleep and a high rate during waking and attention (Sakai et al. 1990). The interactions with orexin neurons (Eriksson et al. 2001; Huang et al. 2001) further indicate that histamine is required for arousal. Orexin is a peptidergic neurotransmitter affecting feeding and wakefulness, and its deficit has a crucial role in narcolepsy (Chemelli et al. 1999). Several investigations support the idea that the level of arousal affects retention and consolidation of memories (Cahill and McGaugh 1995), thus, neuronal histamine may affect cognitive processes by modulating neuronal functions throughout the brain, according to the animal state. Nevertheless, recent findings indicate that the histaminergic system may also directly influence neurobiological processes underlying learning and memory (Passani et al. 2000; Passani and Blandina 2003).

Histamine Modulates ACh Release From the Amygdala and Emotional Memory in a Bimodal Fashion

Emotional memory may be assessed with adversely motivated training tasks, such as contextual fear conditioning. In this test, the experimental animal learns to associate a mild electrical footshock with the environment in which it receives the punishment. Re-exposure to the same environment will induce, even in the absence of the punishment, a stereotyped behavior, denominated freezing that is characterized by the complete absence of voluntary movements. The time spent freezing during recall is correlated with animal memory ability, as an amnesic animal will spend less time freezing during recall, than a normal one. There is extensive evidence that crucial neural changes mediating emotional memory occur in the basolateral amygdala (BLA; Davis 1992; LeDoux 2000). For instance, fear memory retention is impaired by posttraining inactivation of this area by lidocaine (Dalmaz et al. 1993) or tetrodotoxin (Sacchetti et al. 1999), and the pharmacological manipulation of the BLA with drugs influencing the cholinergic system affects memory consolidation for adverse events (Introini-Collison et al. 1996; Vazdarjanova and McGaugh 1999). The injection of H_3 receptor antagonists/inverse agonists into the BLA decreases the freezing time of trained rats compared with saline-injected controls (Passani et al. 2001), thus causing an amnesic effect (Fig. 2A). Conversely, intra-BLA injection of H_3 receptor agonists augments the freezing time (Cangioli et al. 2002), which is an indication of procognitive effects (Fig. 2A). In these experiments, the drugs were injected immediately after training, and the retention test was carried out after 3 d, thus avoiding any influence on acquisition and/or other processes that indirectly may affect learning (McGaugh and Izquierdo 2000). Hence, H_3-ligands directly modulate fear-memory consolidation processes. Because several studies have shown that manipulation of cholinergic neurotransmission within the BLA affects the expression of memory after fear conditioning (McGaugh 2000), the effects of H_3 ligands on amygdalar ACh release were addressed using the microdialysis technique that allows the collection of extracellular fluid, and the delivery of drugs to very discrete brain areas. Local perfusion with either H_3-antagonists/inverse agonists or H_3-agonists, at concentrations comparable with those that affected fear memory in the behavioral experiments, decrease (Passani et al. 2001) or increase (Cangioli et al. 2002) ACh release from the BLA, respectively (Fig. 2B). Consistent with previous findings (Introini-Collison et al. 1996; Vazdarjanova and McGaugh 1999), these observations stress the importance of BLA cholinergic tone for consolidation of fear memories. Furthermore, they demonstrate that histaminergic compounds modify the expression of fear memories in a bimodal fashion, and modulate the cholinergic tone within the amygdala accordingly. The BLA receives abundant cholinergic innervation from the nucleus basalis magnocellularis (Mesulam et al. 1983; Carlsen et al. 1985), and displays high H_3-receptor binding (Pollard et al. 1993) and expression of its gene transcripts (Lovenberg et al. 1999). H_3 receptors act as inhibitory auto- and hetero-receptors, thus inhibiting histamine synthesis and release as well as the release of other neurotransmitters, including ACh (Blandina et al. 1998; Haas and Panula 2003). In the BLA, H_3 receptor binding is strictly associated with the presence of histaminergic fibers (Anichtchik et al. 2000), and local perfusion with H_3 receptor antagonists/inverse agonists increases endogenous histamine release (Cenni et al. 2003); therefore, the inhibition of ACh release

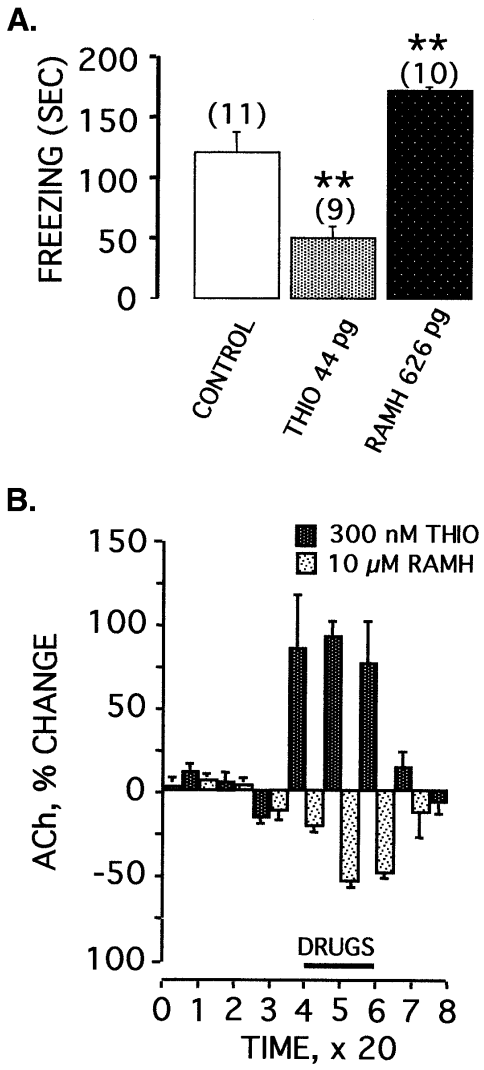

Figure 2 (*A*) Effects of posttraining bilateral injections of an H_3 receptor antagonist (thioperamide) or an H_3 receptor agonist (R-α-methylhistamine/RAMH) into BLA on contextual fear conditioning. Rats were injected immediately after training under general anesthesia (ketamine, 100 mg/kg i.p.). Each drug was freshly prepared and diluted in sterile saline to permit the injection of a constant volume of 0.5 μL/side to each rat. Solutions were injected over a 1–2 min period, and the needle was left in place for another minute before withdrawal. Controls were injected with saline. At 72 h after training, freezing was measured during the first 3-min period of the retesting. Each bar represents the mean value ± SEM of (n) experiments. $^{**}P < 0.01$ vs. control (ANOVA and Neuman-Keuls' test). (*B*) Effect of thioperamide and RAMH on ACh spontaneous release from the BLA of freely moving rats. ACh was measured in fractions collected every 20 min, beginning 2 h after the onset of the perfusion. Spontaneous release of ACh was calculated for each experiment by averaging the mean of the four initially collected 20-min samples of perfusate, and ACh release was expressed as percentage of its spontaneous release value. Mean value of ACh spontaneous release averaged 0.12 ± 0.02 pmole/20 min in the experiments with RAMH ($n = 5$), and 0.26 ± 0.05 pmole/20 min in those with thioperamide ($n = 4$). The bar indicates the period of thioperamide application. Thioperamide (300 nM) or RAMH (10 μM) were administered into the BLA through the dialysis probe; the bar indicates the period of drug application. Shown are means ± SEM of four experiments (thioperamide) and five experiments (RAMH). (Passani et al. 2001; Cangioli et al. 2002, modified).

elicited by H_3-antagonists/inverse agonists could be most simply explained by a blockade of inhibitory H_3 autoreceptors (Fig. 1). Blockade of H_3 autoreceptors augments histamine release in the BLA, which, in turn, moderates cholinergic neurotransmission, presumably by activation of postsynaptic H_2 receptors, as pretreatment with cimetidine fully antagonizes cholinergic inhibition caused by H_3 antagonists/inverse agonists (Passani et al. 2001). The opposite may occur when H_3 receptors are activated. These results are in agreement with the impairing effect of histamine administered into the BLA on the acquisition of an avoidance task (Alvarez and Ruarte 2002). In this learning paradigm, animals are trained in a two-compartment cage with a wall separating the compartments. Animals are conditioned to escape from the punishment box, where they receive a mild foot-shock, to the safe box. The punishment is preceded by an ultrasonic tone, which subsequently will elicit the escape, even without the foot-shock. The latency of escape is an indication of how well the animal remembers. Histamine administered locally to the BLA, increases the escape latency and impairs learning.

The evidence reviewed above renders the histaminergic system one of the conceivable neural bases mediating hypothalamic influences on the storage of emotionally based memories. Furthermore, it may provide the fine-tuning of ACh release necessary to produce the adequate behavioral response.

Histamine Influence on Memory Depends on the Brain Region and the Cognitive Task Involved

Although H_3 antagonists/inverse agonists impair contextual fear conditioning (Passani et al. 2001), their administration produces significant enhancement in several cognitive tasks. Pharmacological blockade of H_3 receptors in the adult rat significantly improves social memory (Prast et al. 1996), enhances attention as evaluated in the five-choice, serial-reaction time test (Ligneau et al. 1998), and improves cognitive performance in the five-trial inhibitory avoidance task (Fox et al. 2002, 2003). Procognitive effects of H_3 receptor antagonists/inverse agonists have been observed also in cognitively impaired animals. For example, thioperamide significantly improves the response latency in a passive avoidance response in senescence-accelerated mice, characterized by a marked age-accelerated deterioration in learning tasks (Meguro et al. 1995). Consistently, two H_3 receptor antagonists/inverse agonists, thioperamide, and clobenpropit, fully reverted scopolamine-elicited impairments in a passive avoidance response and object-recognition test in the rat (Giovannini et al. 1999). Similarly, FUB 181, an H_3 receptor antagonist (Stark et al. 1998), significantly ameliorates performances of scopolamine-impaired mice in the elevated plus-maze test (Onodera et al. 1998). Cognitive performance is also improved in spontaneously hypertensive rat (SHR) pups challenged in a five-trial avoidance test, following administration of A-304121 or A-317920. These are non-imidazole compounds of particular interest for clinical application, because of a lower potential for metabolic interactions and receptor-binding promiscuity than most known antagonists/inverse agonists of the H_3 receptor (Hough 2001; Esbenshade et al. 2003). Juvenile SHR rats are normotensive, but exhibit many cognitive impairments (Fox et al. 2002, 2003). Because these deficits are genetic in origin, this model appears more clinically relevant than those requiring additional pharmacological or surgical intervention.

In rats, as in humans, projections from the NBM provide the majority of cholinergic innervation to the cortex (Mesulam et al. 1983; Heckers et al. 1994). Both in vitro (Clapham and Kilpatrick 1992; Arrang et al. 1995), and in vivo (Blandina et al. 1996) experiments demonstrated that locally applied histamine decreases the cholinergic tone in the cortex through activation of H_3 receptors. This interaction may have functional relevance, as systemic administration of H_3 receptor agonists impairs rat per-

formance in object recognition, and in a passive avoidance response at the same doses that reduced ACh release from freely moving rat cortex (Blandina et al. 1996). This was the first evidence that related the cognitive effects of histamine to modifications of ACh neurotransmission, and agrees with the observations that reduced availability of ACh in the synaptic cleft results in cognitive deficits (Quirion et al. 1995). H_3 receptor-induced inhibition of cortical ACh is abolished in cortices in which the traffic of action potentials was blocked by tetrodotoxin (Blandina et al. 1996), thus strongly suggesting that H_3 receptors modulating cortical ACh release are located postsynaptically on intrinsic perikarya (Arrang et al. 1995). Microdialysis experiments demonstrated that immepip, an H_3 receptor agonist, increases GABA release from the cortex of freely moving rats, and bicuculline, a GABAA receptor antagonist, reverses the inhibition of ACh release induced by immepip (Giorgetti et al. 1997). Thus, it is conceivable that H_3 heteroreceptors facilitate GABA release, which, in turn, inhibit ACh release. Cortical GABAergic interneurons control the activity of large populations of principal cells through their extensive axon arborization (Freund and Meskenaite 1992). Therefore, any pathway, even if relatively sparse, such as the histaminergic pathway, may exert a powerful effect on the activity of the cortex if it modulates the activity of local GABAergic interneurons. The observation that H_3 receptor agonists moderated ACh release and impair cognition (Blandina et al. 1996), by inference, may account for the procognitive effects of H_3 receptor antagonists reviewed above. Yet, in this regard, another observation may be relevant. Histaminergic modulation of cortical cholinergic tone appears to be complex, and consists of two components, one inhibitory, related to local actions at the terminals, the other excitatory, resulting from interactions with cholinergic cell bodies in the NBM (Fig. 1). The administration of H_3 antagonists/inverse agonists, such as clobenpropit or thioperamide into the NBM, increased the output of ACh from the cortex of rats implanted with two microdyalisis probes, one in the NBM to locally deliver the different drugs, and the other in the cortex to measure the output of ACh (Cecchi et al. 2001). H_3 autoreceptors appear to be involved, because perfusion of rat NBM with the same compounds elicit a local increase of endogenous histamine (P. Blandina, unpubl.). Pretreatment with triprolidine fully blocks the effect of thioperamide on cortical ACh release (Cecchi et al. 2001), thus implicating postsynaptic H_1 receptors. This finding is consistent with a report that histamine depolarizes the membrane and increases the tonic firing of guinea-pig nucleus basalis magnocellularis cholinergic neurons through H_1 receptor activation (Khateb et al. 1995). Further, rats that received i.c.v. administrations of the selective H_1 receptor agonist 2-(3-(trifluoromethyl)-phenyl)histamine performed better than saline-injected animals in the object-recognition task (Malmberg-Aiello et al. 2003). On the other hand, the performance in attention-demanding tasks deteriorates after treatment with H_1 receptor antagonist at doses that fail to cause changes in subjective sleepiness (Okamura et al. 2000). The evidence reviewed above supports the hypothesis that activation of the dense histaminergic innervation to the NBM facilitates the cholinergic tone in the cortex. Working memory tasks, as well as noncognitive stimuli, such as stress or sensory stimulation (Pepeu and Blandina 1998), activate the cortical circuitry that requires ascending excitatory influx from the brainstem, involving several neurotransmitters such as ACh, GABA, glutamate, histamine, and noradrenaline (Nicoll et al. 1990; McCormick and Williamson 1991). The NBM cholinergic system, which plays an important role in cortical activation (Steriade and Buzsaki 1990), may therefore represent the final pathway of several inputs (Pepeu and Blandina 1998). These interactions may have implications for cognitive decline associated with aging and Alzheimer's disease. The different degrees of degeneration of various transmitter systems and their possible mutual compensatory effects may account for individual differences in cognitive capabilities. In fact, aging is not necessarily associated with alterations of learning and memory abilities (Rapp and Amaral 1992), and different levels of impairment are observed in Alzheimer's disease. Interestingly, binding of H_1 receptors, assessed by positron emission tomography, is significantly decreased in the brain of Alzheimer's disease patients compared with those of normal subjects (Higuchi et al. 2000), thus revealing a disruption of the histaminergic neurotransmission in this pathology. The characteristic cortical cholinergic dysfunction may result from cell degeneration of both cholinergic and noncholinergic neurons of the NBM (Whitehouse et al. 1982), and from reduction in impulse flow from the NBM to the cortex (Aston-Jones et al. 1985). Loss of cholinergic neurons would reduce the cortical cholinergic activity directly, yet degeneration of noncholinergic neurons may contribute to cholinergic hypofunction. These observations can be readily integrated; loss of NBM GABA neurons (Gritti et al. 1997), which project primarily to cortical GABA interneurons (Freund and Meskenaite 1992), would increase the cortical GABAergic inhibitory tone on ACh release (Giorgetti et al. 2000). Also, the decrease of excitatory inputs to the NBM cholinergic neurons, because of the reduction of H_1 receptors, may contribute to the cortical cholinergic hypofunction.

Not Only Cognition: Interactions Between Histaminergic and Cholinergic Neurons Affect Arousal

Diminished alertness, slowed reaction times, and somnolence are common manifestations of treatments with H_1 antagonists, thus suggesting that histamine is required for arousal. The evidence became persuasive with the report that histidine decarboxylase knockout mice, which lack histamine, display increased paradoxical sleep, cortical-EEG changes, sleep-wake cycle modifications, and are unable to remain awake when high vigilance is required, such as at light-off or during environmental changes (Parmentier et al. 2002). Furthermore, orexin seems to have an important role in sleep regulation (Mignot et al. 2002), and the arousal effects of the orexin system depends on the activation of the histaminergic neurons (Huang et al. 2001). The interplay between the two systems was also demonstrated in orexin receptor-2 mutated, narcoleptic dogs; these animals have significantly lower levels of histamine in the cortex and thalamus, whereas other neurotransmitter systems are unaffected (Nishino et al. 2001). Cortical activation (EEG desynchronization) is one of the salient signs of wakefulness and requires high cholinergic, histaminergic, noradrenergic, and serotonergic tones (Mignot et al. 2002). Histaminergic neurons activate the cortex directly via their widespread hypothalamo-cortical projections or, indirectly, by stimulating the serotonergic raphe neurons (Brown et al. 2002). In addition, they activate the cholinergic corticopetal system originating from the nucleus basalis magnocellularis (Cecchi et al. 2001) and the substantia innominata (Lin et al. 1994). Also, cholinergic projections to the thalamus and the hypothalamus are critical to cortical activation, complementing the direct cholinergic projections from the basal forebrain to the cortex. Histaminergic-descending afferents excite cholinergic neurons in the mesopontine tegmentum, which, in turn, projects to the thalamus and the hypothalamus, thus eliciting cortical activation through thalamo- and hypothalamo-cortical circuitries (Lin et al. 1996). The excitatory interactions between histaminergic and cholinergic neurons in the basal forebrain, the hypothalamus, and the mesopontine tegmentum constitute a crucial mechanism within the ascending neuronal network responsible for the maintenance of cortical activation and wakefulness.

Concluding Remarks

A wide variety of studies agree that the neuronal histaminergic system interacts with cholinergic neurons to regulate arousal and some forms of cognition.

Our understanding of both physiological and pathological mechanisms of sleep and cognitive disorders requires learning the neural basis of these functions. In addition to histaminergic and cholinergic neurons, other neurotransmitter systems are certainly implicated, although it is not known to what extent. This is particularly true for arousal, in which the hypothalamus plays a key role; hypothalamic neurotransmitter systems (adenosine, dopamine, GABA, histamine, and orexin) along with extrahypothalamic cholinergic systems provide the framework for most models of sleep regulation (Mignot et al. 2002). The information obtained from these studies may have therapeutic applications for treating sleep disorders. Concerning cognition, interactions between the histaminergic and cholinergic systems serve as one of the physiological correlates of the ability of animals to learn and remember (Passani et al. 2000; Bacciottini et al. 2001; Passani and Blandina 2003). Treatment strategies of cognitive impairments have traditionally been aimed at restoring the cholinergic neurotransmission, yet therapies with cholinesterase inhibitors or muscarinic agonists have been generally unproductive, as the improvements of cognitive functions are generally modest and confined to a minority of patients (Kelly 1999). One explanation could be that cholinergic drugs used in most clinical trials produce a greater stimulation of inhibitory autoreceptors, either by increasing the half-life of ACh in the synaptic cleft (Davis et al. 1992), or by directly activating these receptors (Gauthier et al. 1991). Histamine receptors could represent the target for compounds, which, taking advantage of noncholinergic mechanisms potentiate cholinergic functions, and may produce beneficial effects on disorders in which the cholinergic function is compromised. Yet, ACh/histamine interactions are complex and multifaceted, and the results are often contradictory, as both facilitatory and inhibitory effects of histamine on memory have been described (Blandina et al. 1996; Passani et al. 2001; Cangioli et al. 2002). The precise timing of histamine release, the distinct actions that the histaminergic system might exert by activating different receptor subtypes, the architectural constraints that separate groups of transmitters in particular brain structures, and the nature of the cognitive task used may determine whether histamine has facilitatory or inhibitory effects. As it turned out, histaminergic H_3 receptor activation, for instance, modulates ACh release and cognitive processes, apparently with modalities that differ according to their role as auto- or heteroreceptors (Blandina et al. 1996; Cecchi et al., 2001; Passani et al. 2001; Cangioli et al. 2002). Thus, it will be necessary to develop drugs not only selective for the receptor subtypes, but also specific for the particular brain region of interest. Multiple mRNA isoforms for the H_3 receptor have been described in rats, guinea pigs, and humans (Tardivel-Lacombe et al. 2000; Coge et al. 2001; Drutel et al. 2001; Wellendorph et al. 2002). Functional receptor isoforms of the H_3 receptor display different pharmacological profiles (Wellendorph et al. 2002), and are distributed in the CNS in a heterogeneous fashion (Drutel et al. 2001). Thus, there is increasing interest, and great effort is being channeled into developing ever-more selective agonists, inverse agonists, pure antagonists for the H_3 receptor, as well as ligands for its various isoforms. This will be a great challenge for the molecular pharmacology in the years to come. Obviously, new discoveries create tremendous expectations, as these compounds have potential ameliorating effects in disorders such as Attention Deficit/Hyperactivity Disorder, Alzheimer's Disease, Mild Cognitive Impairment, and anorexia as proposed elsewhere (Leurs et al. 1998; Passani and Blandina 2003).

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