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Selective histamine H_3 receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous system

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Abstract

Evidence exists to implicate the monoamine histamine in the control of arousal and cognitive functions. Antagonists of H_3 receptors are postsynaptic and presynaptic modulators of neural transmission in a variety of neuronal circuits relevant to cognition. Accumulating neuroanatomical, neurochemical, pharmacological, and behavioral data support the idea that H_3 receptor antagonists may function to improve cognitive performances in disease states (e.g., Alzheimer's disease and mild cognitive impairment states). Thus, H_3 receptor antagonists have been shown to increase performance in attention and memory tests in nonhuman experiments and prevent the degradation in performances produced by scopolamine, MK-801, or age. In contrast, agonists of the H_3 receptor generally produce cognitive impairing effects in animal models. The role of H_3 receptors in these behavioral effects is substantiated by data indicating a central origin for their effects, the selectivity of some of the H_3 receptor antagonists studied, and the pharmacological modification of effects of H_3 receptor antagonists by selective H_3 receptor agonists. Data and issues that challenge the potential role for H_3 receptor antagonists in cognitive processes are also critically reviewed. H_3 receptor antagonists may also have therapeutic value in the management of obesity, pain, sleep disorders, schizophrenia, and attention deficit hyperactivity disorder.

Keywords: Histamine; H_3 receptors; Cognition; Attention deficit hyperactivity disorder; Schizophrenia; Review

Abbreviations: A-304121, 4-(3-((4-((2*R*)-2aminopropanoyl)-1-piperazinyl)propoxy)phenyl)(cyclopropyl)methanone; A-317920, *N*-((1*R*)-2-(4-(3-(4-(cyclopropylcarbonyl)phenoxy)propyl)-1-piperazinyl)-1-methyl-2-oxo-ethyl)-2-furamide; A-331440, 4′-[3-(3(*R*)-(dimethylamino)-pyrrolidin-1-yl)-propoxy]-biphenyl-4-carbonitrile; ABT-418, (*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole; ACh, acetylcholine; ADHD, attention deficit hyperactivity disorder; α-FMH, α-fluoromethylhistidine; AQ0145, *N*-(1-adamantyl)4-(4(5)-imidazolyl)piperidine-1-methaneimine; BP 2.94, (*R*)-*N*-(2-hydroxy-α-phenylphenylmethylidine)-2-(4(5)-imidazolyl)-1-methylethylamine; ciproxifan, cyclopropyl-(4-(3-(1H-imidazol-4-yl)propyloxy)phenyl) ketone; CNS, central nervous system; FUB 181, 4(5)-{3-[3-4-(chlorophenyl)phenoxy]propyl}-imidazole; GT2016, analogue of GT2331; GT2331, (cipralisant)-4-((1*R*,2*R*)-2-(5,5-dimethyl-1-hexynyl)cyclopropyl)-1H-imidazole; RAMH, *R*-α-methylhistamine; tele-MeHA, tele-methylhistamine; VUF 9153, clobenpropit.

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The therapeutic control of cognition remains an important and complex challenge. Patients suffering from mild cognitive impairment, Alzheimer's disease, and cognitive impairments from a host of other insults such as schizophrenia, Parkinson's disease, and neural trauma are all potential candidates for improved therapies. Several compounds are in development beyond the discovery phase for cognitive indications (Table 1). Table 1 highlights that (1)

Table 1
Major compounds in development for cognitive indications

Compound (trade name) [sponsor]	Mechanism	Therapeutic indications	Furthest development
Donepezil (Aricept) [Eisai, Pfizer]	Acetylcholinesterase inhibitor	Alzheimer's disease, vascular dementia, ADHD	Launched worldwide
Galantamine (Reminyl) [Janssen]	Acetylcholinesterase inhibitor	Alzheimer's disease	Launched worldwide
Tacrine (Cognex) [First Horizon]	Acetylcholinesterase inhibitor	Alzheimer's disease	Launched worldwide
Rivastigmine (Exelon) (Novartis)	Acetylcholinesterase inhibitor	Alzheimer's disease	Launched worldwide
Memantine (Ebixa) [Merz, Forest, Lundbeck]	NMDA antagonist	Alzheimer's disease, vascular dementia, AIDS dementia	Used in Europe, launched in the United States
TAK 147 (Zanapezil) [Takeda]	Acetylcholinesterase inhibitor	Alzheimer's disease	Phase III
Nefiracetam (Tranlon) [Diichi]	Calcium channel agonist	Alzheimer's disease, vascular dementia	Phase III
Nimodipine (Nimotop) [Bayer AG]	Calcium channel antagonist	Alzheimer's disease, cerebral infarction	Phase III
Celecoxib (Celebrex) [Pharmacia/Pfizer]	COX-2 inhibitor	Alzheimer's disease progression/prevention	Phase III
Metrifonate [Bayer]	Acetylcholinesterase inhibitor	Alzheimer's disease	Reached phase III
Cipralisant [Gliatech, Merck]	H_3 antagonist	Dementia, insomnia, obesity	Reached phase II
Phenserine [Axonyx]	Acetylcholinesterase inhibitor	Alzheimer's disease	Phase II
MKC 231 or Colurecetam [Mitsubishi]	Choline uptake enhancer	Alzheimer's disease, amnesia, stroke	Phase II
T-588 [Toyama]	Stimulates monoamine release	Alzheimer's disease, vascular dementia	Phase II
NS-2330 [NeuroSearch/Boehriger Ingelheim]	Enhances monoamine availability	Alzheimer's disease	Phase II
NGD-971 [Neurogen/Pfizer]	Negative GABA modulator	Alzheimer's disease	Phase II
SB-271046 [Galaxo SK]	Serotonin-6 antagonist	Cognitive impairment	Phase II
Atorvastatin [Lipitor] [Pfizer]	HMG CoA reductase inhibitor	Alzheimer's disease progression/prevention	Phase II
Aniracetam [Roche]	Transmitter release modulator	Cognitive impairment, stroke	Phase II
CX-516 (Ampalex) [Cortex/Servier]	AMPA receptor modulator	Alzheimer's disease, mild cognitive impairment, ADHD	Phase II
ABT-089 [Abbott]	Nicotinic cholinergic	Alzheimer's disease, ADHD, schizophrenia	Phase I
ABT-239 [Abbott]	H_3 antagonist	Cognitive disorders	Phase I
ABT-834 [Abbott]	H_3 antagonist	Cognitive disorders	Phase I
SCH-211803 [Schering]	M_2 antagonist	Alzheimer's disease	Phase I
CEP-1347 [Cephalon]	JNK inhibitor	Alzheimer's disease progression/prevention	Phase I
CPI-1189 [Centaur]	MAPK inhibitor	Alzheimer's disease, AIDS dementia	Phase I

Compounds in the later stages of development are listed as the information about them is better substantiated than those in phase 1 and earlier. Not all compounds are shown for the earlier phases. Data are from the Investigational Drug Database (February 2004).

there are many compounds in this landscape, (2) there are several compounds already on the market (primarily acetylcholinesterase inhibitors), (3) many compounds are in clinical phases of development (preclinical stage molecules are not shown), (4) the compounds have diverse mechanisms of action, and (5) they include the H_3 receptor antagonists from Gliatech and Abbott.

The present review examines the evidence that H_3 receptor blockade may have therapeutic utility in cognitive deficiency disease states. The attention that has been expended on the discovery of therapeutics for these disorders based on this mechanism is clear from a review of the scientific and patent literature as well as a look at the compounds in development as shown in Table 1. In addition to cognitive deficiency states, data on the therapeutic potential of histamine H_3 receptor antagonists for obesity, epilepsy, attention deficit hyperactivity disorder (ADHD), sleep disorders, narcolepsy, and pain will also be reviewed.

1. Histamine neurobiology and pharmacology

1.1. Histamine

It is now well established that histamine functions as a neurotransmitter in the brain (Wada et al., 1991; Schwartz et al., 1994), confirming the suggestion by Green (1964). The physiology of brain histamine is the subject of extensive recent literature reviews (Brown et al., 2001; Haas & Panula, 2003). Brain histamine originates from cell bodies of the tuberomammillary nucleus of the posterior hypothalamus with projections extending to diffuse brain regions. Indeed, the branching of histaminergic projections in brain resembles that of the dopamine, norepinephrine, and serotonin systems, suggesting, as with these monoamine transmitters, a significant global central coordinating function for histamine over a host of physiological and behavioral processes.

It also seems clear that the activity of histaminergic neurons is tightly coupled to the sleep/wake cycle, being most active during the waking phases and having very low activity during the sleeping phases. An example of this is illustrated by electrophysiological studies in freely moving cats (Vanni-Mercier et al., 2003). Recordings from histaminergic neurons in the tuberomammilary nucleus showed highest activity during the active waking stage, less activity during quiet waking, very low activity during slow wave sleep stage 1, and essentially no activity during slow wave sleep stage 2 or paradoxical sleep stages. Consistent with this are studies using in vivo microdialysis to measure histamine release in the brain showing that histamine release is highest during the waking phases in both cats (Strecker et al., 2002) and rats (Mochizuki et al., 1992). The coupling of histaminergic neuronal activity and histamine release to specific phases of the sleep/wake cycle is a factor that should be taken into account when planning or interpreting data from experiments that use pharmacological manipulation of histaminergic receptors.

Histamine, whether released by neurons or mast cells, produces its effects in tissues by interacting with G protein-coupled receptors. To date, 4 separate histamine receptors have been cloned and characterized. These have been designated H_1, H_2, H_3, and H_4 (for reviews of H_1, H_2, and H_3, see Hill et al., 1997; Leurs et al., 2000; for H_4, see Nakamura et al., 2000; Oda et al., 2000; Liu et al., 2001; Nguyen et al., 2001). The H_3 receptor, which is the focus of this review, appears to be primarily localized in the central nervous system (CNS; see discussion below). In contrast, the H_4 receptor, which shows some pharmacological overlap with the H_3 receptor, appears to be primarily localized in the periphery, especially in immune cells.

1.2. H_3 receptors

H_3 receptors are G_i/G_o-coupled receptors regulating the influx of calcium ions that are critical to histamine release (Arrang et al., 1983, 1995; Hill & Straw, 1988). Additional second messenger systems and transduction pathways have been described (see Hancock et al., 2003 and below). H_3 receptors are primarily CNS receptors (however, see Hancock et al., 2003 for a review of the earlier data on peripheral tissue localization). Confusion around their distribution has occurred because the commonly used pharmacological tools that were thought to be H_3 selective also have equivalent affinity for the more recently cloned H_4 receptor, which may normally exist only in the periphery (cf. Zhu et al., 2001). H_3 receptors function as autoreceptors to control the release of histamine in the CNS (Arrang et al., 1983, 1987) as well as its synthesis (Arrang et al., 1987). In addition, H_3 receptors control the release of a host of other central neurotransmitters (Schlicker et al., 1994; Brown et al., 2001). Thus, H_3 heteroreceptors have been shown to regulate release of dopamine, norepinephrine, and serotonin in brain slice preparations (Schlicker et al., 1988, 1989, 1993; Smits & Mulder, 1991). H_3 receptors also tonically regulate release of acetylcholine (ACh; see review by Bacciottini et al., 2001). Agonists inhibit release of ACh in vitro and in vivo (Clapham & Kilpatrick, 1992; Arrang et al., 1995; Blandina et al., 1996). The mechanism of ACh release appears to be through γ-aminobutyric acid (GABA) interneurons in the cortex (Giorgetti et al., 1997), amplifying on the theme of histamine as a broad coordinator of cortical activity.

Cloning of H_3 receptors has been achieved in rat (Lovenberg et al., 2000; Morisset et al., 2000; Drutel et al., 2001), guinea pig (Tardivel-Lacombe et al., 2000), mouse (Chen et al., 2003), rhesus monkey (Yao et al., 2003a, 2003b), and human (Lovenberg et al., 1999; Wellendorph et al., 2002).

H_3 receptors exhibit high constitutive activity that is demonstrated by the dose-dependent enhancement of histaminergic function in vivo by H_3 receptor antagonists/inverse agonists such as thioperamide and cyclopropyl-(4-(3-(1H-

imidazol-4-yl)propyloxy)phenyl) ketone (ciproxifan; Ligneau et al., 1998; Morisset et al., 2000).

The presynaptic localization of H_3 receptors and their function as autoreceptor/heteroreceptor regulators of neurotransmitter release enables neurotransmitter measurement as a means of establishing functional H_3 receptor blockade at specific synapses. Measurements of tele-methylhistamine (tele-MeHA), the primary metabolite of histamine in brain (Schwartz et al., 1971), have been used for monitoring of terminal fields of histaminergic neurons such as in the cerebral cortex. Increases in tele-MeHA reflect increases in histamine turnover. Such increases also demonstrate the tonic inhibition normally played by the endogenous neurotransmitter on histaminergic neuronal firing and histamine release. It must be noted, however, that differences between histamine H_3 receptor antagonists in their effects on tele-MeHA levels have been reported (Yates et al., 1999b; Barnes et al., 2001). The differential effects of some ligands on metabolite levels may be due to their differential ability to reduce histamine methylation (Barnes et al., 2001). The significance of these differences for defining differential pharmacological activities of compounds has not been uncovered.

Subtypes of the H_3 receptor have been suggested (West et al., 1990; Drutel et al., 2001; Wellendorph et al., 2002), and the data surrounding the subject of receptor heterogeneity of histamine H_3 receptors have been reviewed (Hancock et al., 2003). Drutel et al. reported 3 functional isoforms of the rat H_3 receptor based on sequences found in the rat brain (H_{3A}, H_{3B}, and H_{3C}) and a truncated variant that is nonfunctional (H_{3T}). The isoforms were shown to be differentially coupled to G_i or to the stimulation of p44/p42 mitogen-activated protein kinase (MAPK). Further complexity was suggested by the differential CNS localization pattern of the receptor isoforms. High signal detection of the H_{3A} isoform was notable in the dorsal portion of the dentate gyrus along with high detection levels in CA1 of ventral hippocampus. The predominance of a given receptor isoform in areas regulating cognitive processes raises the possibility for selective pharmacological targeting. However, to date, no isoform selective ligands have been reported. Species differences in the existence of splice variants have also been reported (Yao et al., 2003a, 2003b). With regard to the existence of functional isoforms of the human H_3 receptor, the current situation seems quite muddy. At least 2 groups have reported the cloning of multiple isoforms of the H_3 receptor from different regions of the human brain (Cogé et al., 2001; Wellendorph et al., 2002). On the other hand, other groups have been unable to find transcripts for any isoforms other than the ‘‘long mRNA’’ form in samples of human brain (Liu et al., 2000; Wiedemann et al., 2002).

In addition to the confusion around the number and types of H_3 receptor isoforms that may be expressed in the human brain, there is also confusion regarding the biological activity of the different isoforms. The long mRNA form is usually called the control or standard form for which radioligand binding and in vitro functional assays are determined for comparison with the other isoforms. For some of the isoforms, the nature of the missing regions clearly indicates that even if protein were made from the mRNA, the resulting structure would lack the ability to bind and/or be activated by histamine. In other cases, the functional significance of the missing regions is not clear. Cogé et al. (2001) compared the functional properties of 2 of the isoforms found in human brain with the long form. In a radioligand binding assay, one of the isoforms, which had amino acids missing from transmembrane domain 2, would not bind the radioligand, while the other isoform (missing amino acids in intracellular loop 3) bound radioligand and showed a pharmacological profile very similar to the long isoform. However, this isoform with the changes in intracellular loop 3 could not functionally couple to the activation of second messenger system. Wellendorph et al. (2002) looked at the in vitro functional activity of the long form plus 4 other isoforms. Two of these isoforms were inactive in their test system, while 2 were active and actually demonstrated greater sensitivity to histamine than did the long form. In a recent review of the H_3 receptor, Hancock et al. (2003) have tried to develop a common nomenclature and summary for all of the various H_3 receptor isoforms that have been described in the literature. In addition to the long form (or full-length receptor) of the human receptor, they list 16 isoforms of the human receptor plus 2 polymorphisms of the long form. Obviously, a significant amount of work remains to unravel the potential biological significance of these multiple forms of the H_3 receptor.

Systematic species comparisons have also revealed differences in ligand binding and functional properties that have yet to be fully understood and appreciated (cf. Ireland-Denny et al., 2001; Chen et al., 2003). The absence of binding of the selective H_3 receptor agonist *R*-α-methylhistamine (RAMH) in mouse brain homogenates from H_3 receptor knockout (KO) mice argues for a single gene product (Toyota et al., 2002).

Selective H_3 receptor antagonists have been discovered. The most widely used experimental tool, thioperamide, exhibits good potency and selectivity for H_3 receptors but also has high affinity for H_4 receptors (27.0 nM at human cloned H_4 receptors; Liu et al., 2001). The affinity of thioperamide for human cloned H_3 receptors (58.0 nM) is lower than that described in rat brain homogenates (Lovenberg et al., 2000). Differences in pharmacology between species used in animal models (as in cognition) and humans must be taken into account when making clinical extrapolations. Molecular modeling has begun to make progress in this area (Yao et al., 2003a, 2003b). Toxicities that may be a function of the thiourea portion of the molecule have taken thioperamide off the list of potential clinical candidates. Another antagonist/inverse agonist

Table 2
Potencies of thioperamide and ciproxifan for histamine H_3 receptors to induce histamine release in vitro and to increase levels of tele-MeHA in vivo

Compound	H_3 receptor affinity, rat	Histamine release, rat cortical synaptosomes	tele-MeHA increases, mouse brain
Thioperamide	4.2 (Lovenberg et al., 2000)[a]	4.0 (Arrang et al., 1987)	1.0 (Ganellin et al., 1996)
Ciproxifan	0.7 (Ligneau et al., 1998)[b]	0.5 (Ligneau et al., 1998)	0.14 (Ligneau et al., 1998)

Data are K_i in nM, except for the tele-MeHA data, which are ED_{50} values in mg/kg p.o. in mice.
[a] Compounds were assayed in cloned receptors using [^{3}H]methylhistamine.
[b] Compounds were assayed in rat striatal membranes using [^{125}I]iodoproxyfan.

ciproxifan is also highly potent in vitro and in vivo. Table 2 summarizes a few of the in vitro and in vivo characteristics of these ligands.

2. A role for histamine in cognitive function

Cognition is not a unitary phenomenon as it is a complex of multiple integrated neurological and behavioral activities of which arousal has ample documentation as a key player. Therefore, it has been argued that a compound that positively modulates attention or vigilance would be valuable in correcting cognitive deficiencies for which these functions were reduced.

2.1. Arousal

A critical role for histamine neurons in arousal was hypothesized 25 years ago (Schwartz, 1977), and this remains today as one of the most well-documented coordinating effects of histamine in the CNS. Ablation studies along with pharmacological manipulations to decrease synthesis and release have demonstrated corresponding decreases in wakefulness of cats and rats. Increases in arousal, in contrast, have been demonstrated when histamine levels are augmented through blockade of methylation (inactivation) or through increasing release by H_3 receptor blockade as demonstrated with thioperamide and carboperamide and by ciproxifan (Lin et al., 1990; Monti et al., 1991, 1996; Ligneau et al., 1998). H_3 receptor antagonists promote wakefulness in the electroencephalogram (EEG; increase in proportion of fast rhythms and a decrease in slow wave and paradoxical sleep patterns). Fig. 1 shows a representative sleep/wake histogram scored from EEG recordings from cats. The wake-promoting effects of ciproxifan (0.3 mg/kg) were significantly attenuated by imetit, a H_3 receptor agonist, demonstrating the dependence of H_3 receptors on this effect. The role of postsynaptic histamine as a regulator of the EEG-activating effect of ciproxifan was suggested by the prevention of these effects of ciproxifan by the H_1 antagonist mepyramine (Ligneau et al., 1998). The attenuation of slow wave activity by H_3 receptor antagonists such as ciproxifan is shared by the ADHD treatment drug methylphenidate (Fox et al., 2003). However, the robustness of the effects of H_3 receptor antagonists to decrease slow wave activity in the EEG may be compound dependent. Two novel non-imadazole H_3 receptor antagonists had more modest effects on the EEG of undisturbed adult rats than did ciproxifan (Fox et al., 2003). Further, systemic administration of the H_3 receptor agonist immepip produced significant decreases in cortical histamine efflux in rats but produced minimal effects on the sleep/wake patterns as monitored by EEG and electromyography (Lamberty et al., 2003). A decrease in locomotion and wheel running was reported in H_3 receptor-deficient mice (Toyota et al., 2002). That the wake-promoting effects of thioperamide are

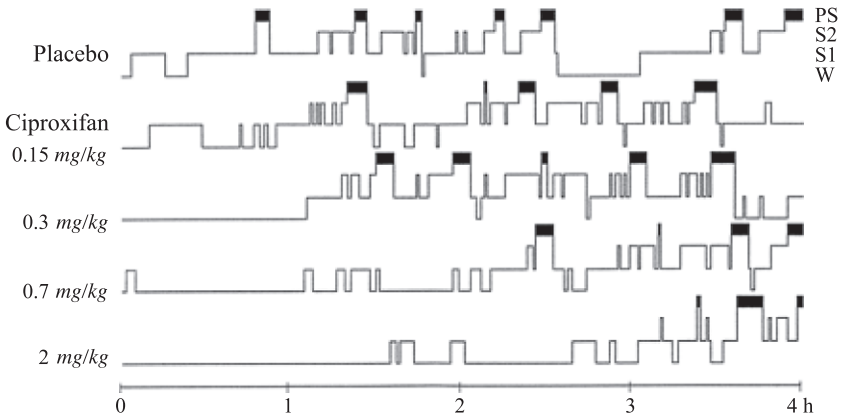

Fig. 1. Dose-dependent increases in wakefulness of cats after oral administration of the H_3 antagonist ciproxifan. Tracings are scored from EEG recordings in nonanesthetized cats. Time is shown on the abscissa over 4 hr. Sleep/wake stages are plotted on the ordinate (PS, paradoxical sleep; S2, deep slow wave sleep; S1, light slow wave sleep; W, wakefulness). Ciproxifan increased wake episode durations and produced an increase in sleep latency. No apparent sleep rebound was noted after the waking effect. From Ligneau et al. (1998) with permission.

absent in H_3 receptor KO mice (Toyota et al., 2002) is confirmatory evidence for the role of this receptor in wakefulness and that it may constitute a reasonable target for drug discovery.

The reported arousal enhancing effects of histamine may be mediated through thalamic neuronal depolarization, which shifts their mode of firing from burst (as in deep sleep) to single spike (predominating during arousal where sensory information is highly efficacious). Other potential neural substrates may also exist. The central activating effects of histamine that can be driven by H_3 receptor blockade may be under the control of H_1 receptors. Data from Ligneau et al. (1998) cited directly above are suggestive of the involvement of this postsynaptic receptor in arousal. In addition, there is a reported reduction in activity levels in H_1 receptor KO mice (Inoue et al., 1996). Further, there is a well-documented sedating effect of compounds that block H_1 receptors.

Although increased arousal could be one component process in enhancing cognitive processing, arousal activation may not necessary. Work with some more recently developed H_3 receptor antagonists has shown that cognitive improvements can be achieved at doses that do not affect arousal as reflected in the EEG of rats. In this work, *N*-((1*R*)-2-(4-(3-(4-(cyclopropylcarbonyl)phenoxy)propyl)-1-piperazinyl)-1-methyl-2-oxo-ethyl)-2-furamide (A-317920) and 4-(3-((4-((2*R*)-2aminopropanoyl)-1-piperazinyl)propoxy)phenyl)(cyclopropyl)methanone (A-304121) enhanced social memory of adult rats for rat pups at doses that did not significantly alter EEG slow wave activity. Moreover, as noted above, these compounds had smaller overall effects on the EEG at higher doses than ciproxifan (Fox et al., 2003).

2.2. Cognition

Data support a role for the neurotransmitter histamine in cognitive functions. Previous reviews of this subject area have been published (cf. Passani et al., 2000; Bacciottini et al., 2001; Schwartz & Arrang, 2002). Evidence comes from multiple sources. Projections of histamine neurons arising from the posterior hypothalamus innervate diverse structures relevant to cognitive function including basal forebrain, cerebral cortex, cingulate cortices, amygdala, and thalamus and through cholinergic projections to hippocampus. The excitatory actions of histamine on some of these "cognitively relevant" projection sites have been documented (see Brown et al., 2001), where there has been ample physiological and behavioral evidence to implicate histamine in arousal functions as summarized above. Moreover, direct or indirect activation of brain histamine has been shown to have cognitive enhancing effects (see review by Passani et al., 2000). For example, in a social memory test with rats, increases in brain histamine facilitate whereas decreases in brain histamine impair social memory (Table 3).

Table 3
Effects of modulations in brain histamine in rats in a test of social memory

Compound	Change in brain histamine	Effect on short-term memory
Histamine (i.c.v.)	↑ [a]	Facilitation
Histidine (i.c.v.)	↑	Facilitation
α-FMH	↓	Decrement
Immepip	↓ [a]	Decrement
Thioperamide	↑ [a]	Facilitation

Data are summarized from Prast et al. (1996). Facilitation in short-term recognition memory was indicated by decreases in the time spent by an adult in investigation of a previously encountered juvenile; a decrement in recognition memory was indicated by increases in investigation times.

[a] Refers to the putative effects on brain histamine that were not directly measured as they were after the histamine precursor, histidine, or the histamine synthesis inhibitor, α-FMH.

Interactions of histamine with the *N*-methyl-D-aspartate (NMDA) receptor polyamine site (Bekkers, 1993; Vorobjev et al., 1993), combined with evidence of histamine-induced facilitation of long-term potentiation in rat hippocampal slices by histamine (Selbach et al., 1997), provides additional support for a role of histamine in cognition. However, the direct role of the spermine-sensitive binding of histamine ($EC_{50} = 1.7$ μM; Vorobjev et al., 1993) has been difficult to establish in slice preparations (cf. discussion by Brown et al., 2001). Further, histamine produces changes in brain levels of ACh (summarized elsewhere in this review), a neurotransmitter tightly linked to cognitive function. Finally, effects of the pharmacological manipulation of the H_3 receptor and other histamine receptors as summarized below provide additional support for the role of histamine in cognition.

3. A role for H_3 receptors in cognitive function

3.1. Supportive evidence

There is an enhancement of histamine turnover by H_3 antagonists. The autoreceptor function of histamine H_3 antagonists has been well characterized. For example, as illustrated in Table 2, the H_3 antagonists ciproxifan and thioperamide increase histamine levels and turnover in brain (Arrang et al., 1987; Ganellin et al., 1996; Ligneau et al., 1998), enabling histamine to exert greater excitatory actions on postsynaptic targets regulating cognition.

H_3 receptor antagonists have shown efficacy in animal models of cognition (see reviews by Passani et al., 2000; Bacciottini, 2001; Schwartz & Arrang, 2002). For example, prevention of passive avoidance deficits from scopolamine or age has been reported with the H_3 antagonist 4(5)-{3-[3-4-(chlorophenyl)phenoxy]propyl}-imidazole (FUB 181; Onodera et al., 1998). Thioperamide improved the deficits in passive avoidance in senescence-accelerated mice (Meguro et al., 1995). The H_3 antagonist GT-2227 enhanced the rate of acquisition of a passive avoidance response in rat

pups, an effect shared by methylphenidate (Yates et al., 1999a). In contrast to methylphenidate, however, GT-2227 did not affect locomotor activity of adult rats. There was a facilitation of retention of footshock avoidance in mice with thioperamide (Flood et al., 1998).

The H_3 receptor blocker ciproxifan enhances histamine turnover, induces neocortical arousal in cats, and enhances attention as measured in the 5-choice task in rats. The improvement seen in the 5-choice task was only seen when the task demand was high (short stimulus duration) and the resulting control performances were markedly impaired (<60% with a 0.25 sec stimulus duration and >80% when the stimulus duration was 0.5 sec; Ligneau et al., 1998). The attention-like augmentation by ciproxifan in the 5-choice test has been previously demonstrated with cholinergic agonists (cf. Muir et al., 1994, 1995). In this regard, it is interesting that while nicotine improved performance on the serial reaction time test, it had smaller effects on accuracy when the stimulus durations were brief (Hahn et al., 2002). Although direct comparisons would be required, comparison of results across studies suggests that nicotine may produce enhancements in attentional performance across a broader range of conditions than those produced by H_3 receptor blockade.

The efficacy of H_3 receptor antagonists has generally been achieved at doses without untoward or notable effects on motor behaviors or other observed behaviors. Nonetheless, the predicted therapeutic indices of H_3 receptor compounds may be a function of structure. In one comparative study, Fox et al. (2003) compared minimal effective doses of compounds to enhance acquisition of performance of spontaneously hyperactive rat pups on a repeated trials passive avoidance task to the minimal adverse doses in mice under several tests including hypoactivity, body temperature, posture, seizure activity, righting response, and lethality. The therapeutic index was calculated as the ratio of toxic dose to efficacious dose, where the higher the ratio, the better the predicted side effect liability. All 3 H_3 receptor antagonists facilitated the acquisition of the passive avoidance response (Fig. 2). The protective index values for thioperamide, ciproxifan, and (cipralisant)-4-((1*R*,2*R*)-2-(5,5-dimethyl-1-hexynyl)cyclopropyl)-1H-imidazole (GT2331) were 8, 10, and 18, respectively, whereas A-304121 and A-317920 were 30 and 42, respectively (Fox et al., 2003). Although therapeutic index estimates are best calculated in the same species, the results of this study point to the possibility of designing drugs that block H_3 receptors with cognitive activating potential without negatively impacting other aspects of CNS function measured.

H_3 receptor antagonists have also been reported to prevent the cognitive performance decrements produced by scopolamine or MK-801 (Miyazaki et al., 1995; Blandina et al., 1996; Onodera et al., 1998; Giovannini et al., 1999; Molinengo et al., 1999). In the study by Giovannini et al. (1999), scopolamine-induced deficits were attenuated by administration of thioperamide and clobenpropit (VUF 9153). H_3

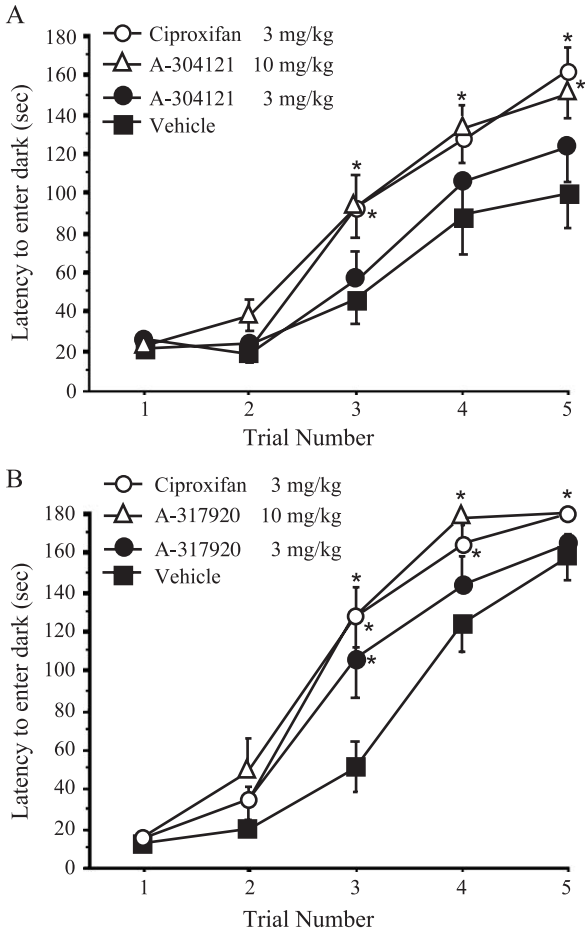

Fig. 2. Enhancement of the acquisition performance under a 5-trial inhibitory avoidance response task in spontaneously hyperactive rat pups with 2 novel H_3 receptor antagonists compared with the H_3 antagonist ciproxifan. (**A**) A-304121 and ciproxifan. (**B**) A-317920 and ciproxifan. Compounds were administered 30 min prior to the first trial. Data are means ± S.E.M. of 12 rat pups. $*P<0.05$ versus the vehicle-treated controls. From Fox et al. (2003) with permission.

receptor-deficient mice showed insensitivity to the amnesic effects of scopolamine in passive avoidance conditioning (Toyota et al., 2002). Intrahippocampal VUF 9153 significantly attenuated the impairment of reference and working memory of rats produced by MK-801 administration in an 8-arm radial arm maze (Fig. 3; Huang et al., 2004).

The cognitive enhancing effects of H_3 receptor antagonists appear to be centrally mediated. H_3 receptor antagonists can be characterized by their ability to inhibit the increases in water consumption of rats engendered by administration of the H_3 receptor agonist RAMH, a centrally penetrant compound (Clapham & Kilpatrick, 1993). That the drinking effect is not peripherally mediated is given credence by the fact that the renin-angiotensin system postulated to be involved in histamine-induced drinking (Kraly et al., 1995) is not involved in the RAMH-induced drinking as evidenced by the lack of affect of blockade of the angiotensin-1 receptor (Clapham & Kilpatrick, 1993). In addition, H_3 antagonists increase levels of the histamine

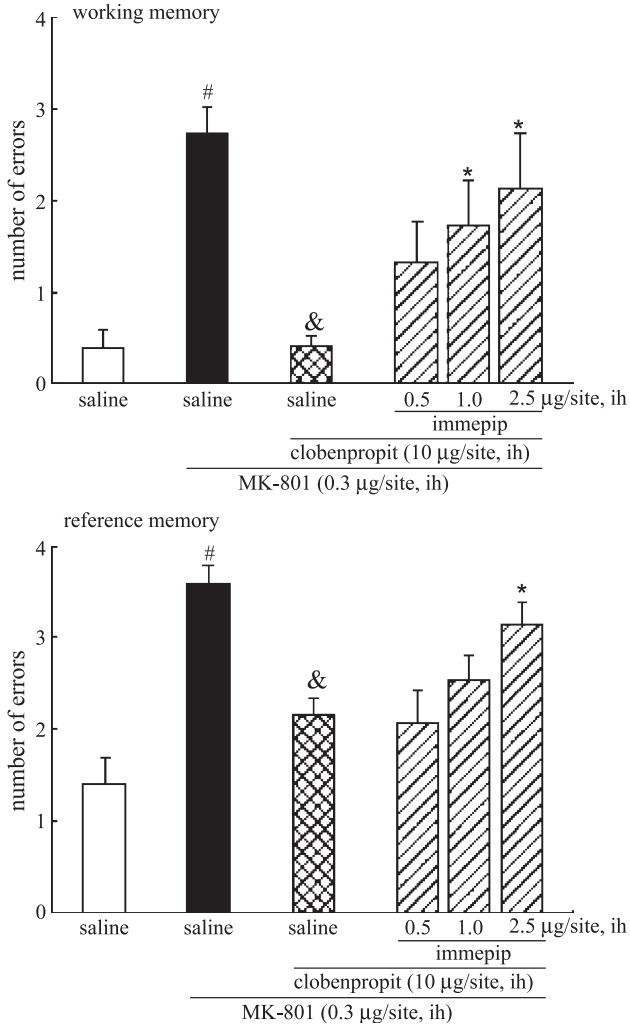

Fig. 3. The facilitatory effect of the H_3 antagonist clopenpropit on working (top panel) and reference memory (bottom panel) as measured in rats in an 8-arm radial arm maze. Also shown is the ability of the H_3 agonist immepip to attenuate the effects of clopenpropit. Each point represents the mean ± S.E.M. of 15–17 rats. $^{\#}P<0.05$ versus the saline-treated group, $^{\&}P<0.05$ versus the MK-801 + saline-treated group, and $^{*}P<0.05$ versus the MK-801 + clopenpropit + saline-treated group. From Huang et al. (2004) with permission.

metabolite tele-MeHA in brain (see Table 2). Finally, there is a positive correspondence between the doses of H_3 receptor antagonists that block RAMH-induced drinking and the doses that enhance brain levels of tele-MeHA (cf. Ligneau et al., 1998). However, as noted earlier, differences between histamine H_3 receptor antagonists in their effects on tele-MeHA levels have been reported (Yates et al., 1999b; Barnes et al., 2001).

Cognitive impairing effects have generally been observed after administration of H_3 receptor agonists. If H_3 receptor antagonists produce their effects on cognitive performances through their actions at histamine H_3 receptors, then H_3 receptor agonists might be predicted to produce cognitive debilitating effects given the constitutive activity in the system. Pretraining but not posttraining administration of the H_3 receptor agonists RAMH or imetit impaired performance of rats in object recognition and passive avoidance. Blandina et al. (1996) showed that these H_3 receptor agonists when given prior to training retarded performance under these tests. The effect of the agonists was produced at doses that decreased the release of ACh in vivo. Posttraining administration of the agonists, on the other hand, did not degrade performance on these tests (Giovannini et al., 1999), suggesting a role of the H_3 receptor in preferentially regulating acquisition over already acquired behaviors. However, other data presented in this review show that H_3 antagonists are also capable of facilitating learned behaviors as well. Further, despite the lack of effect of posttraining administration of the agonists on performance, the degradation in performance produced by scopolamine was prevented by thioperamide (Giovannini et al., 1999). The H_3 agonist immepip also produced cognitive impairing effects in tests of olfactory and social memory (Prast et al., 1996). Imetit and RAMH reduced K^+-stimulated ACh release in cortex, an effect prevented by the H_3 receptor antagonist VUF 9153 but not by the H_1 and H_2 antagonists triprolidine and cimetidine, respectively (Blandina et al., 1996). Symmetry in the effects of compounds on brain histamine in rats and behavioral effects in a short-term memory task based on social olfactory cues was also seen (Table 3). In this work by Prast et al. (1996), a H_3 agonist decreased social memory (increased olfactory investigation time), whereas thioperamide produced the opposite effect.

Pharmacological data support the H_3 receptor as the target for the efficacious effects of H_3 receptor blockers in cognitive tests. Blockade of effects of H_3 antagonists by selective H_3 receptor agonists (e.g., RAMH; Miyazaki et al., 1995) support an H_3 receptor antagonist mechanism of action. MK-801-induced deficits in performance in an 8-arm maze were ameliorated by bilateral intrahippocampal administration of the H_3 antagonist VUF 9153; the protective effects of VUF 9153 were prevented by the H_3 receptor agonist immepip (Fig. 3; Huang et al., 2004). That histamine release was related to the behavioral effects of VUF 9153 was demonstrated by Huang et al. (2004) by showing that the histamine precursor, histidine, potentiated the effects of VUF 9153 and that the selective inhibitor of histidine decarboxylase, α-fluoromethylhistidine (α-FMH), prevented the effects of VUF 9153 on working memory.

Effects at histamine H_1 receptors also support H_3 receptor involvement in cognitive function. Likewise, the prevention of H_3 antagonist effects on cognitive function by H_1 receptor antagonists (Miyazaki et al., 1995, 1997; Molinengo et al., 1999) implicates histamine release via H_3 blockade as the mechanism of action. That this H_1 receptor-mediated effect is central is suggested by the prevention of effects of FUB 181 with the centrally penetrant H_1 blocker ketotifen but not by terfenadine, which does not readily penetrate the CNS. Likewise, (*R*)-*N*-(2-hydroxy-α-phenylphenylmethylidine)-2-(4(5)-imidazolyl)-1-methylethylamine (BP 2.94), a prodrug of the agonist RAMH,

prevented the effects of the H_3 antagonist FUB 181 (Onodera et al., 1998). Further support for a role of antagonist effects at H_3 receptors as a driver of improved cognitive performance comes from the improvement in memory reported with 2-methylhistamine (Bhattacharya, 1990), a selective H_1 receptor agonist. A role for H_1 receptors as targets for histamine in the control of cognition has also gained support from others (cf. Malmberg-Aiello et al., 2000). That H_1 receptors may function as a postsynaptic target for histamine to improve cognition is also supported by the data from the effects of H_1 receptor antagonists as sedating and cognitively impairing (cf. Passani et al., 2000).

Actions of H_3 antagonists to augment ACh levels in brain may be one of the drivers of cognitive enhancement. Reduced levels and function of ACh in brain are thought to be a major contributor to age-related cognitive deficits. Choline uptake is reduced in the elderly (Cohen et al., 1995). The increased levels of histaminergic activity in aging human brain (Prell et al., 1988, 1991) and increased levels of histamine in rat brain with age (Onodera et al., 1992) may be contributing factors to the decreased ACh uptake and function. Thus, H_3 antagonists, by virtue of their ability to prevent these cognitive- and ACh release-impairing effects of histamine at H_3 receptors (cf. Blandina et al., 1996), could be a means of facilitating ACh function through a novel mechanism. Thus, thioperamide facilitated ACh release in rat cortical slice preparations (Clapham & Kilpatrick, 1992) and in hippocampus of anesthetized rats (Mochizuki et al., 1994). Thioperamide delivered to the nucleus basalis magnocellularis of rats, an area providing prominent cholinergic input to the cerebral cortex, facilitated place learning in a Y maze (Orsetti et al., 2002). Cholinergic innervation to the hippocampus arises from the medial septum diagonal band. In vivo microdialysis studies in freely moving rats have demonstrated increases in extracellular ACh levels in hippocampus with thioperamide and ciproxifan delivery into the medial septum diagonal band, whereas the H_3 agonist RAMH produced the opposite effect (Bacciottini et al., 2002).

3.2. Challenging data and issues

Improvement of learning and memory with functional impairment of tuberomammillary histamine neurons have been reported (Huaton et al., 1997). These data are consistent with the findings of H_3 agonist-induced decreases in cognitive performances noted above. However, if histamine H_3 receptor antagonists facilitate cognitive processing by initiating histamine-driven events in the brain through their autoreceptor function, these facilitatory findings of lesions may be at odds with this hypothesis. How can these lesion data be reconciled with the other findings? The improvements reported may be due to sparing from excitotoxin destruction or deactivation. The specificity with which histaminergic pathways were impacted also must be raised. The H_3 receptor antagonist may act on a subset of projection neurons, and through this interaction, histamine may facilitate cognition. The remaining projection pathways may, in contrast, be inhibitory to cognitive function. In addition, because H_3 receptors are presynaptically localized on non-histaminergic neurons, the lesion data do not directly address the modulation of cognition by H_3 antagonists. The data on the role of the H_3 receptor are thus most strongly supported by the data on the effects of selective antagonists reviewed above.

Although H_3 agonists have been reported to be detrimental to cognitive performance, enhancement in performance has also been reported. Thus, RAMH was reported to facilitate spatial learning in a water maze test (Smith et al., 1994). Such apparent discrepancies may be due to the specific neuronal systems underlying spatial learning, which relies on hippocampal function in contrast to attentional functions or episodic memory functions that may involve additional neural control processes. This idea is supported by dissociation experiments including lesion studies. Here, basolateral/cortical lesions dramatically disrupt behaviors in tests of passive avoidance, olfactory, and social memory as well as object recognition memory while only marginally impairing spatial learning in the water maze (Jäkälä et al., 1993). Although these arguments appear compelling, they are put to some test with pharmacological data indicating that scopolamine-induced memory impairment in a radial arm maze is attenuated by VUF 9153, an effect that is antagonized by RAMH (Chen, 2000). As noted earlier, the constitutive activity of H_3 receptors must be kept in mind. The impact of this constitutive activity as it impacts heteroreceptor function and the relationship this may play with the sleep/wake patterns of histamine neurons (see Section 1 above) is only beginning to be appreciated.

H_3 receptor antagonists do not uniformly show efficacy all in animal models of cognition. Thioperamide did not improve the scopolamine-induced deficits in elevated plus maze learning in mice (Miyazaki et al., 1995), and neither thioperamide nor VUF 9153 significantly improved degraded performances under passive avoidance testing (Miyazaki et al., 1995, 1997). In addition, scopolamine-induced deficits in a 5-choice attention test in rats were not attenuated by thioperamide (Kirkby et al., 1996), whereas ciproxifan was able to enhance performance in this task that had been degraded by shortening the attention stimulus duration (Ligneau et al., 1998). Recent reports of the lack of activity of thioperamide and clopenpropit in novel object recognition tests in both wild-type and Apoe-null mice appear to be confounded by the fact that testing was conducted under conditions where vehicle-treated mice were spending more time exploring the novel object and no positive control was studied (Bongers et al., 2004). The ability of compounds to enhance performance in such tests is typically observed after delays in stimulus presentations such that baseline performance is not optimal. Nonetheless, data from Bongers et al. (2004) demonstrated a negative influence of these H_3 receptor antagonists under normal conditions that will

require additional data to fully appreciate. In addition, these investigators reported enhanced anxiety-like effects in the elevated plus maze that will also require additional investigation to best place these data in the context of their predicted clinical implications.

Other data have more clearly shown that under conditions in which thioperamide or VUF 9153 did not show cognitive improvement in object recognition or passive avoidance tests when administered prior to training to normal animals, both compounds relieved the cognitive impairing effects of scopolamine (Giovannini et al., 1999). This is not to say that under similar conditions, however, that H_3 antagonists cannot improve both normal and scopolamine effects on memory (cf. Molinengo et al., 1999). That thioperamide is producing more general reversal of cognitive impairment than that induced by cholinergic blockade is demonstrated by the attenuation of the cognitive deficit on radial arm maze performance produced by the NMDA receptor ion channel antagonist MK-801 (Chen et al., 1999; Huang et al., 2004).

Although H_3 antagonists are not universally positive in efficacy in cognitive tests, sometimes hints of their latent activities have been reported. For example, thioperamide and clopenpropit, not significantly efficacious in their own right, significantly improved scopolamine-induced deficits in mice when given in conjunction with the H_2 receptor antagonist zolantidine (Miyazaki et al., 1995, 1997). Although FUB 181 was effective at a higher dose, a lower ineffective dose had significant effects when given with zolantidine (Onodera et al., 1998). These later findings suggest that the lack of efficacy sometimes reported with H_3 antagonists may be due to the influence of postsynaptic H_2 receptors. The implications of these data are that the efficacy of H_3 antagonists is going to be braked by the histamine effects at these sites. However, discordant data exist on this point as zolantidine has also been reported to block the cognitive enhancing effects of thioperamide, whereas pyrylamine did not (Orsetti et al., 2001). H_2 receptor antagonists also appear to have opposing actions to those of H_3 antagonists in the basolateral amygdala. Ciproxifan, thioperamide, and VUF 9153 decrease ACh efflux in this brain area in freely moving rats, and the H_2 antagonist cimetidine had a small effect in the opposite direction. Cimetidine antagonized the effect of the H_3 antagonists on ACh efflux in this brain area (Passani et al., 2002).

The limited data on H_2 receptor involvement in cognition are that the agonist 4-methylhistamine worsens memory (Bhattacharya, 1990), whereas the H_2 antagonist zolantidine improves cognitive performances when given in conjunction with thioperamide or VUF 9153 (Miyazaki et al., 1995, 1997). In contrast, zolantidine was not effective in preventing improved cognitive performance engendered by FUB 181 (Onodera et al., 1998). From these data and the data on H_1 receptor involvement already described, the simplistic hypothesis can be put forward that one of the potential mechanisms through which H_3 antagonists produce their positive effects in cognition is by relieving the presynaptic constraint of histamine availability by blocking the autoreceptor. Histamine thus made available postsynaptically produces procognitive effects through interaction with H_1 receptors (which may be transduced through interactions with the cholinergic system) and by an inhibitory effect on cognition through H_2 receptors. The contradictory data of Orsetti et al. (2001), however, must be considered before a definitive role for H_2 receptors can be ascribed. In addition, the fact that different brain structures engage the histamine system in different ways to operate on cognitive processes needs to be more fully mapped (see discussion in Section 3.3 below).

The data from H_3 receptor KO mice may not be indicative of a general change in cognitive status. Although H_3 receptor KO mice were not impaired by scopolamine in passive avoidance testing, they were not different from wild-type controls in their response to scopolamine in another test of memory that measures habituation of exploratory behavior to an open field (Toyota et al., 2002). Habituation under these conditions can be arguably debated as to its merits as a measure of cognition. Nonetheless, these data, along with the lack of consistency with which H_3 receptor antagonists affect behavior under a range of methods designed to assess cognitive processing, point to the possibility that H_3 receptor antagonists may affect specific subsets of cognitive functioning. The different effects of the H_3 receptor gene deletion on scopolamine-induced memory impairments suggested that H_3 receptors may be particularly sensitive to cognitive processing and recall when aversive stimuli are involved (see Section 4.6 below). In addition, the reduction in the locomotor stimulant effects of scopolamine in these mice may reflect a more general modulation of the cholinergic system in the absence of H_3 receptors than a specific effect on memory per se.

The effects of H_3 antagonists on cognitive function are modulated by the conditions under which they are studied. The effects of H_3 receptor antagonists, like that of other compounds that affect behavior, are modified by the prevailing environmental contingencies and aspects of control performance (cf. Witkin & Katz, 1990). For example, effects of thioperamide on memory consolidation were shown to depend on whether noxious stimulation was present during the test (Molinengo et al., 1999). Thioperamide has also been shown to affect memory of mice when a memory deficit is produced but not to affect memory of nonimpaired mice (Passani et al., 2000). That deficits in memory or attention may be essential for H_3 antagonists to exert enhancing effects was also seen in the experiments in the 5-choice attention task in which ciproxifan reversed the impairments observed under ‘‘difficult’’ (rapid stimulus presentation) but not under less difficult task demands (Fig. 4; Ligneau et al., 1998). Furthermore, Meguro et al. (1995) reported improvement in cognitive performance of senescence-accelerated mice but not of normal aging mice.

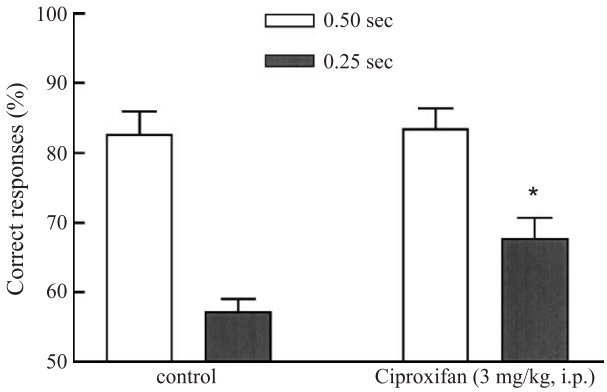

Fig. 4. Ciproxifan (3 mg/kg i.p.) facilitated performance of a 5-choice attention test in rats. Baseline accuracy and the ability of ciproxifan to facilitate performance was dependent on the duration of the stimulus signalling which response would be reinforced (the correct response). Data are means ± S.E.M. $*P<0.05$ versus the vehicle-treated controls. From Ligneau et al. (1998) with permission.

Taken together, these data suggest that H_3 receptors may serve an active role in cognitive processing and in associated ACh release most prominently under conditions of impaired functioning.

The time of administration of H_3 blockers with respect to behavioral training and testing has also been shown to be a determinant of their procognitive effects. For example, in the study by Orsetti et al. (2001), postacquisition administration of thioperamide facilitated memory of previously learned behavior. In contrast, thioperamide given prior to the test was ineffective. In this test situation, thioperamide appeared to facilitate memory by augmenting memory consolidation perhaps through increases in arousal or more specific aspects of the process. Facilitation of memory consolidation by H_3 antagonists has been discussed earlier by other experimenters as well (Blandina et al., 1996; Ghi et al., 1998; Giovannini et al., 1999). Nonetheless, manipulations of central histamine have also been shown to affect both consolidation (de Almeida & Izquierdo, 1986; Kamei et al., 1993) and retrieval of memory (Kamei & Tasaka, 1993) in avoidance conditioning paradigms. In the study by Kamei and Tasaka, it must be noted that the H_3 antagonist thioperamide was not effective. Whereas many of the reports in the literature have used conditions under which H_3 antagonists were given during or after training, efficacy has also been reported when the H_3 antagonist is given during cognitive testing itself. For example, ciproxifan was efficacious in the 5-choice attention test (Fig. 4; Ligneau et al., 1998). The precise aspects of cognition on which histamine acts to transduce its beneficial effects are not at present clear. It must also be remembered that measurement of the pharmacological modification of cognition is by necessity intimately tied to the behaviors on which the tests are based. The effects of compounds on "other" behaviors may interfere with the expression of behavioral effects that may be indicative of enhanced cognition. Another issue raised by the data on "consolidation" is the potential for the compound to produce its effects through state-dependent learning mechanisms wherein the drug effect on "memory" is only revealed when the training state and the testing state are the same (e.g., when compound is administered both during training and during testing; cf. Izquierdo, 1989). State-dependent effects of thioperamide were specifically ruled out in experiments by Orsetti et al. (2001).

The dose-effect curves for H_3 receptor antagonists in animal models of cognition are typically not monotonic. Indeed, generally a narrow range of doses produces improvement. Although such U-shaped or inverted U-shaped functions also occur with a host of other putative and clinically used cognitive enhancers (cf. Gold, 1989) and although the nonlinearity may be due to the intrusion of other behavioral effects not specifically pertinent to cognition per se, such dose-effect data make prediction of clinical efficacy and the design of clinical trials more cumbersome. That the lack of linearity comes from multiple central activities of the H_3 receptor antagonists is suggested by the comparable efficacy achieved in a shock avoidance retention test by thioperamide when delivered locally across doses of 50–400 ng per septum in rats (Flood et al., 1998).

3.3. A model of H_3 receptors in cognition

Based on the data summarized above in animal models of cognition, very primitive hypotheses can be rendered to describe the cascade of events from ligand binding to secondary neurotransmitter processing to cognitive-like performance changes. Histamine arising from the hypothalamus impinges broadly on brain areas involved in cognitive function and performance. Histamine operates on H_1, H_2, and H_3 receptors that may activate cognitive circuits. Blockade of the H_3 autoreceptor augments histamine levels at these postsynaptic histamine receptor targets. The data to date most strongly implicate the actions of histamine at postsynaptic H_1 receptors in producing cognitive facilitation in animal models with systemically administered H_3 receptor antagonists. However, some data also suggest an involvement of H_2 receptors. In other cases and depending on the brain area, H_3 heteroreceptors modulate the firing of neurons that either indirectly and/or directly impact neuronal circuits involved in cognition. Thus, H_3 receptors on GABA interneurons modulate ACh levels in the cortex. Here, H_3 receptor blockade results in augmented ACh release and generally a concurrent facilitation of cognitive performances. In other brain areas, in contrast, H_3 receptor antagonists negatively influence ACh release (e.g., basolateral amygdala) and produce cognitive performance impairments when delivered locally to this site. Some of the discrepancies in the literature on the effects of H_3 receptor antagonists in cognitive models may well be related to the different brain sites involved, although no simple model can be deduced from the literature on systemic drug administration.

The region-specific nature of the response to H_3 receptor ligands is best illustrated by the work in the basolateral amygdala. At doses of the H_3 antagonists that decreased ACh efflux, these compounds impaired contextual fear conditioning as did scopolamine (Passani et al., 2002). In contrast, infusion of the H_3 receptor agonists RAMH and immepip into this central site resulted in the opposite effect on ACh efflux and improved the consolidation of fear conditioning (Cangioli et al., 2002). Thus, in contrast to the general hypothesis that histamine H_3 receptor antagonists could function to facilitate cognitive processing or to reduce the deficits produced by insults to the system, these data show that the opposite prediction is made at least for fear conditioning at the level of the basolateral amygdala; here, H_3 receptor agonists are enabling.

Based on the data at hand, it has been hypothesized that H_3 antagonists may be effective in some behavioral models of cognition through their ability to increase levels of ACh in relevant brain regions. Data on the relationship of histaminergic and cholinergic neuronal circuits in cognition have been nicely summarized previously (Bacciottini et al., 2001) and are represented in Fig. 5.

Although there is ample support for this model, there is not always a perfect correspondence between cognitive improvement and changes in ACh function. For example, the H_3 blocker FUB 181 blocked scopolamine-induced learning deficits in mice; however, ACh and choline levels in cortex, diencephalon, midbrain, cerebellum, or pons/medulla were not affected. Levels are not a measure of functional activity; apparently, transmitter turnover was indeed increased but not measured. Another potential answer to this disparity in behavioral versus neurochemical data is that FUB 181 is not a selective H_3 receptor ligand. VUF 9153 did not modify the release of ACh in freely moving rats, a result that may be explained by the lack of tetrodotoxin (TTX) sensitivity to ACh release under these conditions (Blandina et al., 1996).

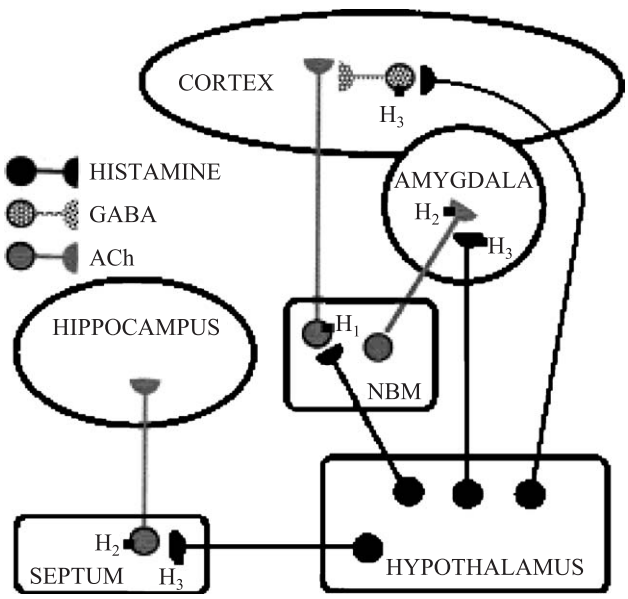

Fig. 5. A schematic representation of the interactions of histaminergic and cholinergic projections that may be relevant to the modulation of cognitive function by H_3 receptor ligands. H_3 receptor ligands may interact with autoreceptors in the septum and the amygdala and thereby modulate the cholinergic tone in the amygdala and hippocampus. H_3 receptor ligands may also interact with postsynaptic sites in the cortex to influence cholinergic tone. From Bacciottini et al. (2001) with permission.

The role of other neurotransmitters controlled by H_3 receptors is much less known in relationship to cognitive performance effects such that no cogent speculation on their specific roles can be reasonably made at present. Nonetheless, the ability of histamine via the H_3 receptor and H_3 antagonists to modulate the synaptic availability of a host of neurotransmitters (cf. Schlicker et al., 1994) including glutamate (cf. Brown et al., 2001), GABA (Garcia et al., 1997; Yamamoto et al., 1997), norepinephrine (cf. Di Carlo et al., 2000), serotonin (Miyazaki et al., 1997; Son et al., 2001), dopamine (Molina-Hernandez et al., 2000), and neurohormones such as vasopressin and oxytocin (cf. Knigge et al., 1999b) is not a meager armamentarium for complex and subtle control of the cognitive processing systems of the CNS. In addition, the secondary and tertiary biological cascade mechanisms that may be involved in activation of H_3 receptor-mediated events such as the ERK pathways (cf. Blandina et al., 2001; Drutel et al., 2001) must not be overlooked.

4. Other potential therapeutic indications for H_3 receptor antagonists

Due to the diffuse distribution of histamine in the brain and to the fact that histamine H_3 receptors control the release of histamine and other neurotransmitters, the therapeutic utility of H_3 receptor antagonists may be quite broad.

4.1. Schizophrenia

The dose-dependent and complete blockade of amphetamine-induced increases in locomotor activity by thioperamide and by ciproxifan (Morisset et al., 2002) suggest a potential use of H_3 antagonists in the treatment of schizophrenia. The locomotor stimulant effects of methamphetamine are also reduced but not completely absent in mice with deletions of the H_3 receptor gene (Toyota et al., 2002). Amphetamines increase tele-MeHA levels apparently as a compensatory response to dopaminergic stimulation (cf. Ito et al., 1996). Increases have been reported in caudate, putamen, nucleus accumbens, hypothalamus, and cortex (Morisset et al., 2002). Moreover, basal levels of tele-MeHA levels are augmented in methamphetamine-sensitized rats (Morisset et al., 2002), a model of schizophrenia. Likewise, tele-MeHA levels in cerebral spinal fluid have also been reported to be elevated in schizophrenic patients (Prell et al., 1995). However, the role of increased histamine turnover in

schizophrenia remains to be clarified. If histamine turnover is directly linked to schizophrenic-like symptomatology, then increases in turnover with a H_3 antagonist may be contraindicated. Further evidence for a potential role of H_3 receptor antagonists in the treatment of schizophrenia comes from data showing a potentiation of haloperidol-induced hypolocomotion and catalepsy and associated neurochemical alterations (e.g., enhanced up-regulation of enkephalin mRNA) by ciproxifan (Pillot et al., 2002). These later data add to the evidence for H_3/D_2 receptor interactions in the CNS.

New data have shown that the H_3 antagonists VUF 9153 and thioperamide can potentiate the ability of methamphetamine to function as a reinforcer or discriminative stimulus in rats and to augment the increases in extracellular levels of dopamine in the shell of the nucleus accumbens in rats (Munzar et al., 2004). In this latter study, however, the H_3 antagonists were not active when given alone. The data from Munzar et al. (2004) indicate again that a dopaminergically driven system can be affected by H_3 receptor blockade.

Data from antipsychotic treatments suggest instead that increases in tele-MeHA turnover may be related to their beneficial effects perhaps in the cognitive arena. Thus, only antipsychotics with good affinity for 5-HT_{2A} receptors increase histamine turnover as measured by tele-MeHA, an effect mediated by 5-HT_{2A} receptor blockade (Morisset et al., 1999). If the histamine turnover inducing effects of atypical antipsychotics is related to their efficacy, then H_3 antagonists due to their intrinsic ability to increase histamine turnover in brain may also have efficacy in the treatment of some symptoms of schizophrenia (e.g., cognition).

4.2. Wakefulness

Narcolepsy is a disorder in which electrophysiological and behavioral sleep occurs during normal waking hours. The disorder is treated symptomatically with CNS stimulants such as methylphenidate, amphetamines, and pemoline. The use of these agents requires careful medical monitoring, and their efficacy is limited by tolerance. The wake-promoting agent modafinil is used in the treatment of narcolepsy. This compound has recently been shown to increase extracellular levels of histamine in hypothalamus of anesthetized rats, although the mechanism appears to be through indirect activation of the histaminergic system (Ishizuka et al., 2003). Nonetheless, these data provide additional validation that H_3 receptor antagonists will promote states of wakefulness in humans. Cataplexy, a correlate of rapid eye movement (REM) sleep, is treated with drugs most effective in reducing REM sleep such as the monoamine oxidase inhibitors and tricylic antidepressants. The partial efficacy of these compounds against cataplexy and sleep paralysis suggests augmentation of noradrenergic transmission as their mechanism of action.

Due to the arousal and sleep controlling nature of histamine (see Section 2.1 above) and histamine's relationship to the arousal-inducing effects of orexin (Huang et al., 2000) make it compelling to venture that H_3 antagonists may have a therapeutic benefit in disorders of this nature. H_1 receptor antagonists are well known for their sedating effects. In contrast, the augmentation of brain histamine levels due to the blockade of the H_3 autoreceptor could then act on H_1 receptors to produce opposing effects as has been illustrated above. Data from mice devoid of histidine decarboxylase, the sole enzyme responsible for histamine synthesis, point strongly toward a necessary role of histamine in the control of sleep/wake patterns (Parmentier et al., 2002). Because environmental stimuli that increased wakefulness, arousal, and attentiveness in normal mice had little effect in the mice that could not synthesize histamine, histamine would also appear to be essential to normal regulation of attentional and arousal processes required for cognitive performances. Histidine decarboxylase KO mice have also been studied with the H_3 antagonist ciproxifan. Ciproxifan engendered bouts of wakefulness in wild-type mice but was devoid of effect in the KO mice (Parmentier et al., 2002). As noted earlier in this review, the activity of the tuberomammilary histamine projections are dependent on the phase of the sleep/wake cycle (Vanni-Mercier et al., 2003) as is the degree of histamine efflux (Mochizuki et al., 1992; Strecker et al., 2002).

4.3. Attention deficit hyperactivity disorder

ADHD is a prevalent disorder that includes in its spectrum of symptomatologies attentional and learning problems. The current treatment for this disorder is with the psychomotor stimulant methylphenidate, which facilitates monoamine efflux via blockade of transmitter uptake (Pliszka, 2001). Recently approved for use is atomoxetine, a selective inhibitor of norepinephrine uptake. There is mounting reason to consider H_3 receptor antagonists as potential candidates for the treatment of ADHD. Firstly, there exists, as summarized above, evidence that H_3 antagonists are predicted to relieve attentional and cognitive deficiencies. Secondly, arousal may be a key component to ADHD arising from hypothalamic dysfunction (Peled et al., 1997). Histamine antagonists may hold promise in clinical practice because of the role of histamine as a primary neural regulator of arousal. Finally, animal models of ADHD have been established that attempt to simulate attentional deficits and hyperactivity (e.g., Shaywitz et al., 1984; Cornwell-Jones et al., 1989; Sagvolden et al., 1992; Sagvolden, 2000). As with methylphenidate, the H_3 antagonist GT2016 (analogue of GT2331) improved passive avoidance behavior in rat pups at doses that are relevant to H_3 receptor antagonism as determined by receptor occupancy and augmented histamine release in cortex in vivo (Tedford et al., 1995; Tedford, 1998). Fox et al. (2002a, 2002b) have contributed a comprehensive package of data on the effects of H_3 antagonists in an analogous animal model. With spontaneously hypertensive

rats that are used in ADHD modeling (Sagvolden et al., 1992; Sagvolden, 2000), repeated behavioral testing on an inhibitory avoidance task with pups produced slower acquisition in performances compared with Wistar or Wistar-Kyoto rats. Methylphenidate and (*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole (ABT-418), clinically effective agents for ADHD, as well as the H_3 antagonists GT2331 and ciproxifan enhanced the acquisition of this inhibitory learning task (see also Fig. 2). The effects of ciproxifan were prevented by RAMH, confirming an H_3 receptor mechanism for the effects of these compounds in this model. In another study, thioperamide was shown to significantly enhance performance under the repeated acquisition of the passive avoidance test (Komater et al., 2003). However, in contrast to methylphenidate, thioperamide did not produce locomotor sensitization or show cross-sensitization to the locomotor stimulant effects of amphetamine or cocaine. In addition, subchronic treatment with methylphenidate increased plasma levels of adrenocorticotropic hormone (ACTH), whereas thioperamide did not. These findings point to the potential therapeutic efficacy of H_3 receptor antagonists for ADHD without dopaminergic or neuroendocrine liabilities.

4.4. Obesity

The high density and localization of H_3 receptors in hypothalamus immediately points to a potential for their role in the regulation of feeding. Interconnections between orexin and histaminergic projections also demonstrate a role for histamine in the regulation of feeding (Eriksson et al., 2001). Decreasing brain histamine by inhibition of histidine decarboxylase with α-FMH has been shown to induce feeding (Sakata et al., 1991; Ookuma et al., 1993). Conversely, histamine (i.c.v.) or thioperamide (i.c.v.) decreases feeding in rats, an effect that is prevented by blockade of H_1 but not H_2 receptors (Ookuma et al., 1993; Lecklin et al., 1998). Histamine can also regulate behaviors associated with food intake. For example, histamine (i.c.v.) decreases the hyperactivity of rats that is engendered by food deprivation that was suggested to bear on the condition of anorexia nervosa (Endou et al., 2001).

That increased synaptic availability of histamine produced by H_3 receptor antagonists is relevant to the histaminergic control of feeding is given additional credence from data demonstrating increases in feeding with H_1 antagonists (cf. Sakata et al., 1991). Bombesin-induced satiety was shown to be regulated by H_3 receptors (Merali & Banks, 1994). In male Sprague-Dawley rats, GT-2227 produced small increases (0.3- to 0.5-fold) in hypothalamic histamine release with corresponding appetite suppression (Nalwalk et al., 1997).

Recent work has shown that a novel H_3 receptor antagonist 4′-[3-(3(*R*)-(dimethylamino)-pyrrolidin-1-yl)-propoxy]-biphenyl-4-carbonitrile (A-331440) reduced body weight comparably with dexfenfluramine in mice, reduced body fat, and produced a normalization in the insulin tolerance test (Hancock et al., 2004).

4.5. Pain

There is also some evidence to suggest a role for H_3 receptors in pain perception. H_3 receptor antagonists have been reported to engender antinociceptive effects (Malmberg-Aiello et al., 1994, 1997). In this work, a role for histamine in pain elicited by mechanical, chemical, and thermal stimuli was demonstrated in mice and rats. Thioperamide produced small but significant antinociceptive effects by both parenteral and i.c.v. routes. Further, the selective H_3 receptor agonist RAMH was hyperalgesic and also prevented the effects of thioperamide. Additional studies with the H_3 antagonists impromidine and burimamide showed limited antinociceptive efficacy that was prevented by RAMH (Lamberti et al., 1996). However, the role of H_3 receptors in pain perception is far from clear. Systemic administration of the H_3 receptor agonist immepip produced antinociceptive effects measured in rat to mechanical but not to thermal stimuli. Thioperamide was able to prevent this effect. Intrathecal immepip produced antinociceptive effects in wild-type but not in H_3 receptor-deficient mice. Localization studies by this group strongly suggested a spinal localization of the effects of the H_3 receptor agonists (Cannon et al., 2003).

4.6. Stress and depression

A role for histamine in response to stress has been suggested. For example, amitriptyline partially prevented the increase in plasma corticosterone and prevented the decrease in [^{3}H]histamine binding sites engendered by footshock in rats (Ghi et al., 1995a, 1995b). The release of histamine in prefrontal cortex elicited by handling was antagonized by intracortical administration of RAMH and potentiated by thioperamide (Westernik et al., 2002). Effects of other stress hormones (ACTH and prolactin) were also dampened by administration of H_3 receptor agonists, an effect prevented by thioperamide (Knigge et al., 1999a). The facts that brain histamine levels are increased under some conditions of stress and that H_3 antagonists augment histamine brain levels and enhance performance in a host of models of cognition are congruent with the data that a certain level of stress or arousal is a positive modulator of behavioral performance. However, histamine is augmented in brain with stress, and the benzodiazepine anxiolytics and the anxiolytic 5-HT_{1A} receptor agonist buspirone decrease histamine turnover in rodents (Oishi et al., 1986, 1992; Chikai et al., 1993), suggesting that increases in central histamine with H_3 antagonists could push the system too far and exacerbate existing anxiety.

H_3 receptor antagonists may also have efficacy as antidepressants. Like the tricyclic antidepressants imipramine

and amitriptyline, thioperamide has been reported to decrease immobility in the mouse forced swim test, a model of behavioral despair with high predictive validity for antidepressant efficacy in humans. However, the effects of thioperamide were not dose dependent as were those of the tricyclic compounds. Nonetheless, the effects of thioperamide were prevented by RAMH (Lamberti et al., 1998).

4.7. Epilepsy

Although a role for histamine in epilepsy has been known for many years (cf. Scherkl et al., 1991), more recent findings have shown that H_3 antagonists like thioperamide, VUF 9153, and *N*-(1-adamantyl)4-(4(5)-imidazolyl)piperidine-1-methaneimine (AQ0145) can decrease acute electrically driven convulsions in mice, an effect that can be prevented by the H_1 antagonist mepyramine (Yokoyama et al., 1993, 1994; Murakami et al., 1995). Unreconciled with this finding at present is the reported proconvulsant effect of H_1 receptor antagonists (cf. Sturman et al., 2001). Thioperamide has also been reported to prevent pentylenetetrazole-induced seizures in mice (Vohora et al., 2000). VUF 9153 given i.c.v. was shown to delay the progression of seizure kindling induced by pentylenetetrazole in rats. This effect was prevented by the H_3 agonist immepip and by the histidine decarboxylase inhibitor α-FMH (Zhang et al., 2003). Additional work will be needed to establish the robustness of these effects and their generality to other seizure models more predictive of antiepileptogenic effects in humans such as the seizure kindling models where inconsistent findings have been reported in amygdaloid-kindled rats (Kakinoki et al., 1998; Yoshida et al., 2000).

5. Clinical development

Cipralisant (GT2331) was the lead H_3 receptor antagonist under development by Gliatech. Merck purchased the compound, and further development may occur in their hands. Cipralisant was being developed for ADHD, insomnia, anxiety, dementia, and eating disorders including obesity. The compound displays high affinity and selectivity for the H_3 receptor. However, The compound has a 40-fold lower affinity at the human cortical H_3 receptor than the rat equivalent. It also demonstrated high affinities at human α_{2a} ($K_i = 5.8$ nM) and α_{2c} ($K_i = 10.8$ nM) adrenergic receptors and human H_4 histamine receptors ($K_i = 80$ nM; Fox et al., 2002a, 2002b). The Food and Drug Administration granted investigational new drug (IND) approval to initiate phase II trials of GT2331 in ADHD in November 1999. Phase I trials for GT2331 were also completed on healthy volunteers in a double-blind, placebo-controlled study, although no published findings have been presented. It is also important to remember that the intrinsic efficacy of compounds at H_3 receptors continues to be defined with compounds previously characterized as full antagonists but have later been shown to have partial agonist or inverse agonist activity (cf. Fox et al., 2002a, 2002b; Wulff et al., 2002).

6. Potential side effects/concerns surrounding the therapeutic use of H_3 receptor antagonists

Given the impact of histamine in arousal and sleep-related processes and the integral need for sleep for optimal cognitive functioning, the effects of H_3 antagonists on the sleep/wake cycle could be countereffective in a medication for cognitive enhancement.

Effects of H_3 receptor antagonists on mast cell functioning should also be considered. Rozniecki et al. (1999) have examined the effects of the H_3 receptor agonist RAMH and the antagonist thioperamide on rat brain mast cells. In contrast to the protective effects of the agonist, thioperamide enhanced release of serotonin and histamine from neurons and mast cells. Message for H_3 receptors was localized principally in the CNS, and Northern blot analysis revealed little expression in any peripheral tissues (e.g., heart, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, prostate, testis, ovaries, small intestine, colon, stomach, thyroid, lymph node tracheae, and bone marrow; Lovenberg et al., 1999). Indeed, whereas H_3 receptors have been shown to control central mast cell activation, peripheral (peritoneal) modulation of mast cells by H_3 ligands is absent (Rozniecki et al., 1999). The possibility that mast cell effects are due to interaction of nonselective ligands such as thioperamide with H_4 receptors needs to be considered.

Peripheral side effects of H_3 receptor agonists may be a potential issue in tissue with high histamine tone such as in the stomach. Peripheral and central histamine regulate gastric acid secretion. RAMH protects against secretions induced by ethanol, hydrochloric acid, salicylic acid, and stress; the effect on ethanol-induced secretions was also attenuated by central administration of RAMH (Coruzzi et al., 2001). An additional potential issue arises from the possible role of H_3 receptors in modulating norepinephrine release from cardiac sympathetic nerve endings (Koyama et al., 2003). Sympathetic discharge with resultant norepinephrine overflow has been implicated as a major factor relevant to arrhythmic cardiac dysfunction in myocardial ischemia. The findings of Koyama et al. (2003) that cardiac synaptosomes prepared from H_3 receptor KO mice show enhanced norepinephrine release compared with wild-type mice suggests that H_3 receptors may play a protective role in cardiac fiber norepinephrine release. Thus, it will be important to determine, in addition to other usual toxicology concerns, whether H_3 antagonists at doses and regimens used for therapeutics have any of these peripheral liabilities. Finally, as the preclinical data in cognition and most of the other areas of interest have involved acute dosing experiments, understanding of the impact of repeated drug exposure for both efficacy and safety are needed.

7. Summary and conclusions

There is a preponderance of data in the scientific literature supporting a therapeutic role for H_3 receptor antagonists in disorders with associated cognitive dysfunction including ADHD. The evidence suggests that the ability of H_3 antagonists to facilitate histamine turnover in specific brain regions may activate cognitive pathways via actions of histamine on postsynaptic H_1 receptors and other targets. In addition, the histaminergic control of ACh, already a well-documented transmitter in the regulation of cognition, may play an important role in mediating the beneficial effects of H_3 receptor antagonists. H_3 receptor antagonists also control the synaptic availability of other neurotransmitters that are likely to impinge on cognitive processing including norepinephrine, dopamine, GABA, and glutamate. Data also exist, however, that challenge the idea that H_3 receptor antagonists may be effective in disorders involving cognition. The field awaits the discovery of safe H_3 receptor antagonist compounds to bring into the clinic for controlled clinical investigation to put this therapeutic possibility to an ultimate test. There has been a good deal of activity in the discovery area over the past several years, suggesting that an answer may be forthcoming in the not too distant future. In addition to the proposed therapeutic potential in disorders involving cognitive dysfunctions including ADHD, H_3 antagonists may also have a role to play at other therapeutic targets including obesity, epilepsy, pain, and sleep disorders.

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