RESEARCH

CNS Neuroscience & Therapeutics

Histamine Pharmacology and New CNS Drug Targets

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SUMMARY

During the last decade, the identification of a number of novel drug targets led to the development of promising new compounds which are currently under evaluation for their therapeutic prospective in CNS related disorders. Besides the established pleiotropic regulatory functions in the periphery, the interest in the potential homeostatic role of histamine in the brain was revived following the identification of H_3 and H_4 receptors some years ago. Complementing classical CNS pharmacology, the development of selective histamine receptor agonists, antagonists, and inverse agonists provides the lead for the potential exploitation of the histaminergic system in the treatment of brain pathologies. Although no CNS disease entity has been associated directly to brain histamine dysfunction until now, the H_3 receptor is recognized as a drug target for neuropathic pain, sleep-wake disorders, including narcolepsy, and cognitive impairment associated with attention deficit hyperactivity disorder, schizophrenia, Alzheimer's, or Parkinson's disease, while the first H_3 receptor ligands have already entered phase I–III clinical trials. Interestingly, the localization of the immunomodulatory H_4 receptor in the nervous system exposes attractive perspectives for the therapeutic exploitation of this new drug target in neuroimmunopharmacology. This review focuses on a concise presentation of the current "translational research" approach that exploits the latest advances in histamine pharmacology for the development of beneficial drug targets for the treatment of neuronal disorders, such as neuropathic pain, cognitive, and sleep-wake pathologies. Furthermore, the role of the brain histaminergic system(s) in neuroprotection and neuroimmunology/inflammation remains a challenging research area that is currently under consideration.

Introduction

Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous short-acting biogenic amine synthesized from L-histidine through the catalytic activity of the rate-limiting enzyme histidine decarboxylase (HDC, EC 4.1.1.22) [1]. Following its discovery 100 years ago [2], histamine has been one of the most studied substances in medicine for a century, possessing a wide spectrum of activities, including its function in neurotransmission (Fig. 1) [3].

Histamine is synthesized in several cell types of peripheral and central tissues. The classical source of histamine is the pluripotent heterogeneous mast cell where it is stored in cytosolic granules and released by exocytosis to exert several actions in response to various immunological and nonimmunological stimuli [4]. Non-mast cell histamine is derived from numerous sources, indicative examples being gastric enterochromaffin-like cells [5], various types of blood cells [6] and neurons [7,8]. The pleiotropic regulatory character of histamine in cellular events is attributed to its binding to four distinct subtypes of G-protein-coupled receptors (GPCRs), designated H_1, H_2, H_3, and H_4 that are differentially expressed in various cell types [9]. In humans, the endogenous ligand shows low affinity for H_1 and H_2 receptors, whereas its potency on H_3 and H_4 receptors is considerably higher. H_3 and H_4 receptors are most closely related to each other and they have a closer phylogenetic relationship with peptide ligand GPCRs, while they are remotely related to other biogenic amine receptors, including H_1 and H_2 receptors [10].

It is currently accepted that all four subtypes of histamine receptors play as yet ill-defined roles in the central nervous system (CNS) [3]. While data on the contribution of histamine receptors in brain physiology and disease states continue to emerge in the literature [11], the H_3 receptor is a recognized drug target for neuronal diseases, such as cognitive impairment, schizophrenia, epilepsy, sleep-wake disorders and neuropathic pain, and the first H_3 receptor ligands have been taken into clinical studies (Table 1) [cf. 12]. Interestingly, the very recent demonstration of H_4 receptor functional expression in the CNS (Fig. 2) [13] may have

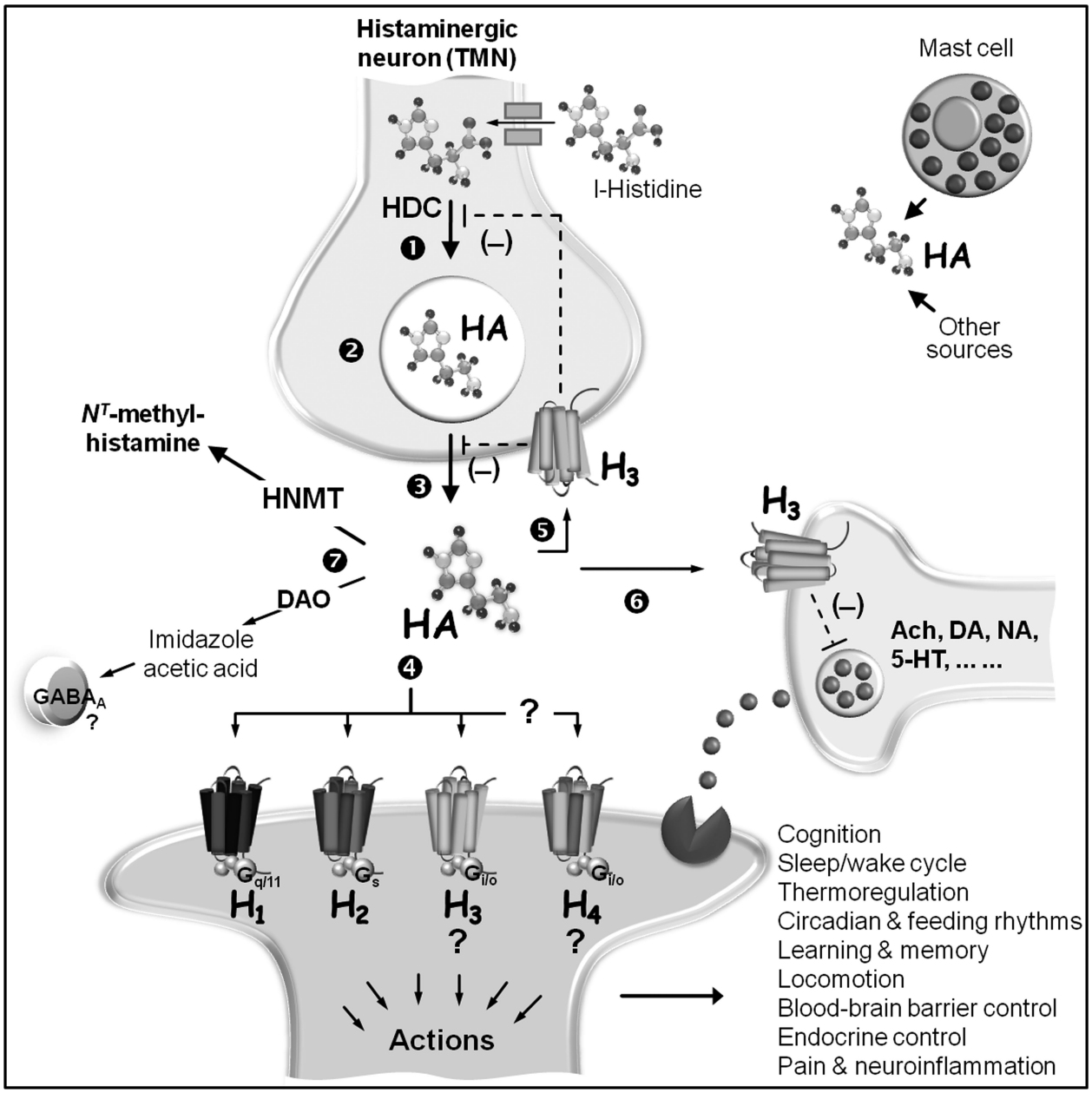

Figure 1 Schematic representation of central histaminergic components. In the adult vertebrate brain, histamine (HA) is formed in histaminergic neurons of the tuberomammillary nucleus (TMN) of the posterior hypothalamus from l-histidine through one-step catalytic action of histidine decarboxylase (HDC) (1). HA is stored in presynaptic secretory vesicles (2), and released into the extracellular space (3) to activate four subtypes of postsynaptic G protein (G)-coupled receptors (4) designated H_1 to H_4, thus eliciting a variety of physiological responses as indicated in the figure. Activation of postsynaptic H_1 receptors has been associated with enhanced vigilance and attention and decreased feeding, while stimulation of the postsynaptic H_2 receptors has been linked to enhanced working memory [18]. Binding to postsynaptic H_3 and, possibly, H_4 receptors leads to as yet poorly defined actions (?), which are currently undergoing rigorous investigation. Stimulation of presynaptic H_3 autoreceptors (5) inhibits (-) HA synthesis (1) and/or release (3), while HA binding to presynaptic H_3 receptors on nonhistaminergic neurons (6) inhibits the release of a number of neurotransmitters, including acetylcholine (ACh), dopamine (DA), noradrenaline (NA), serotonin (5-HT), and others in a pathway-dependent manner. HA is inactivated (7) predominantly by methylation through neuronal histamine *N*-methyltransferase (HNMT), without excluding the contribution of diamine oxidase (DAO) as a salvage pathway to produce imidazole acetic acid, a γ-aminobutyric acid $(GABA)_A$ receptor agonist. Additional sources of brain HA may include (hypothalamic) mast cells and other nonneuronal components [cf. 3].

Table 1 Histamine H_3 receptor ligands in clinical evaluation

Disorder	Compound	Condition	Phase	Study identifier[a]
Narcolepsy	BF2.649	EDS	III	NCT01067222
	BF2.649	Cataplexy (add on Modafinil)	III	NCT01067235
	GSK-189254		II[c]	NCT00366080
	JNJ-17216498		II[b]	NCT00424931
	PF-03654746	EDS	II	NCT01006122
ADHD	MK-0249		II[b]	NCT00475735
	PF-03654746		II[b]	NCT00531752
Alzheimer's disease	GSK-239512	(mild to moderate)	II	NCT01009255
	MK-0249	Cognitive function	I[c]	NCT00874939
	MK-0249		II[b]	NCT00420420
	PF-03654746	(mild to moderate)	I	NCT01028911
Schizophrenia	BF2.649	Cognitive function	II	NCT00690274
	GSK-239512	Cognitive function	II	NCT01009060
	MK-0249	Cognitive function	II[b]	NCT00506077
Parkinson's disease	BF2.649	EDS	II[b]	NCT00642928
	BF2.649	EDS	III	NCT01036139
Neuropathic Pain	GSK-189254	Hyperalgesia	I[b]	NCT00387413

ADHD, attention deficit hyperactivity disorder; EDS, excessive daytime sleepiness; BF2.649, tiprolisant, [1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine hydrochloride] [46,47]; GSK-189254, 6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-*N*-methyl-3-pyridinecarboxamide hydrochloride [54].
[a]www.clinicaltrials.gov.
[b]Completed.
[c]Terminated.

implications for the therapeutic potential of these receptors in central disorders, in addition to their topicality as a potential drug target for inflammatory conditions [14].

The complex brain histamine neurophysiology [3,15,16] and its receptor ligand pharmacology [12,17,18] have been extensively reviewed in the recent literature. This contribution highlights the challenging novel new CNS drug targets introduced by the latest advances in histamine pharmacology, predominantly pertaining to the H_3 and H_4 receptors, and focuses on a concise presentation of the very recent data supporting the "bench-to-bedside" concept and future directions for the potential exploitation of the histaminergic system in the treatment of brain pathologies.

Histamine in the Brain

The presence of histamine in the brain was first shown more than 60 years ago [19,20]. Early indirect pharmacological evidence for the role of histamine in the brain was provided by the sedative side effects of classic antihistamines used for the treatment of allergies and by the interactions, particularly with the H_1-receptor, of a number of drugs commonly used in neuropsychiatry, including typical or atypical antipsychotics and antidepressants [21]. However, research into the significance of histamine in the CNS has been delayed for many decades, as a possible correlation of these interactions to the therapeutic actions of neuropsychiatric medication was overlooked and any histamine-related effects of these agents were regarded solely as side effects resulting from their complex pharmacology [22]. More importantly, the well-established strong association of histamine with peripheral mast cells and with the pathophysiology of atopic diseases [4] seems to have deterred neuroscientists from the investigation of this biogenic amine.

Despite the structural and functional identification of the mostly excitatory H_1 and H_2 receptors in the CNS, the important actions of histamine in the brain were recognized in the 1980s [8,23] in parallel with the identification of H_3 autoreceptors that control the activity of histaminergic neurons [7]. Since then, ongoing related research continues to provide evidence for the (patho)physiological significance of the histaminergic system in the CNS and for a better understanding of the actions of therapeutic agents, such as the H_4 receptor binding of several neuroactive drugs, including amitriptyline and clozapine and the recently identified H_1 receptor-mediated orexigenic actions of the antipsychotic clozapine in the hypothalamus [24].

Histamine does not penetrate the blood–brain barrier; hence its biosynthesis in the brain is elicited in one step by HDC (Fig. 1) and is controlled by the availability of L-histidine [cf. 3]. Unlike other biogenic amines, histamine is not a direct inhibitor of its biosynthetic enzyme, *S*-α-fluoromethylhistidine being a selective and potent HDC "suicide" inhibitor [25]. In the adult vertebrate brain, histamine is formed in histaminergic neurons of the tuberomammillary (TM) nucleus of the posterior hypothalamus that project to all major areas of the brain, whereas data on the afferent connections are relatively limited [3,15]. Neuronal histamine is stored in cell somata and in axon varicosities, while its synthesis and release are controlled mainly through H_3 autoreceptors on the somata, dendrites and axons (Fig. 1). Histamine acts postsynaptically via H_1, H_2, H_3, and H_4 receptors, and it is inactivated by methylation through neuronal histamine *N*-methyltransferase (HNMT,

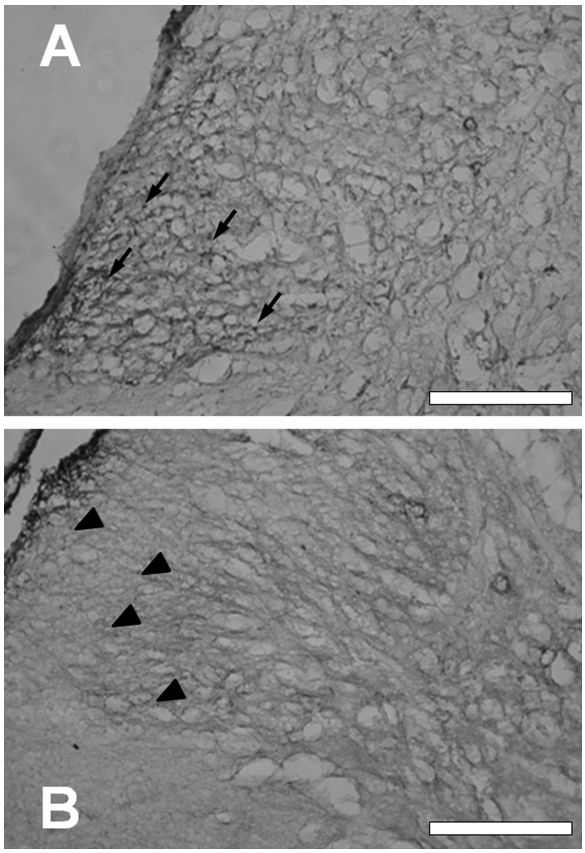

Figure 2 Histamine (**A**) H_3 and (**B**) H_4 receptors expressed in the mouse spinal dorsal horn. Paraformaldehyde (4%)-fixed adult murine spinal cords were dehydrated using sucrose infiltration, with 10% sucrose, then 20% sucrose made up with phosphate buffered saline, and snap-frozen in isopentane −70°C for 1 minute and stored at −80°C. Cryoslices (20 μm thickness) were probed with either (A) anti-H_3 and (B) anti-mH_4 receptor antibodies essentially as described previously [35,38]. Arrows and arrowheads indicate H_3 and H_4 receptor expression, respectively. Bar = 200 μm.

EC 2.1.1.8), without excluding the contribution of diamine oxidase (DAO, EC 1.4.3.6), which converts histamine into imidazole acetic acid, a γ-aminobutyric acid $(GABA)_A$ receptor agonist [cf. Ref. 3].

So far, no direct association between a neuronal disease and brain histamine dysfunction has been identified. In a mutual interaction network with other transmitter systems, brain histamine is implicated in basic homeostatic and higher brain functions, including sleep-wake regulation, circadian and feeding rhythms, body temperature, locomotor activity, learning, and memory [3]. Relatively recently, attention has been drawn to the role of histamine in autoimmune diseases and neuroinflammation [26,27], while H_4 receptors, which are primarily, but not exclusively, distributed in immune cells [10] may be involved in a number of elaborate homeostatic and integrative interactions between the immune and nervous systems.

Besides neuronal histamine, mast cells, which are fundamental in peripheral immune and atopic responses [4], seem to be an additional source of brain histamine (Fig. 1). Mast cells appear to act as gatekeepers at interfaces between the CNS and the endocrine and immune systems [28–31], as they can migrate into the brain, particularly during development [32] and under some pathological conditions [33].

Histamine H_3 Receptors

Studies on histamine function in the CNS have been focused largely on the effects mediated via H_3 receptor signaling [7]. H_3 receptors are located on TM neurons and are mainly expressed in cerebral cortex, hippocampus, amygdala, nucleus accumbens, globus pallidus, striatum, thalamus, and hypothalamus [34,35]. The human H_3 receptor gene is located on chromosome 20q13.33 and encodes a 70 kDa 445 amino acid peptide belonging to the GPCR family [36], showing very low sequence similarity with other GPCRs and only 22% and 20% similarity with H_1 and H_2 receptors, respectively [17]. Downstream signalling is mediated through $G_{i/o}$ proteins and consequently the negative coupling of the receptor to adenylyl cyclase downregulates cAMP-dependent activation of protein kinase A and cAMP-response-element-binding protein-induced gene transcription. Additional interactions with other effector signalling cascades include the activation of phospholipase A_2, as well as the mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways (PI3K), which activate extracellular signal-regulated kinases and Akt and subsequently inhibit the action of glycogen synthase kinase 3β (GSK3β), thus playing important roles in neuronal apoptosis, axonal and synaptic plasticity and being associated with Alzheimer's disease, ischemia or Parkinson's disease, diabetes, and/or insulin resistance [cf. 3,17].

The H_3 autoreceptor function in the negative feedback control of histamine synthesis and release from histaminergic neurons [7], as well as the cross-talk of the H_3 heteroreceptor with other neurotransmitters, including acetylcholine, dopamine, serotonin, and noradrenaline (Fig. 1) [18], play a major role in brain physiology [3], illustrated by the high H_3 receptor constitutive or spontaneous activity *in vivo* [37]. However, H_3 receptors show species differences and pronounced molecular and functional heterogeneity achieved through differential splicing. The large number of isoforms exhibit differential distribution and pharmacological patterns that have complicated the extrapolation of preclinical data into the clinic [17]. The challenge is even greater than initially expected because of the complexity of the central histaminergic system, the diversity of actions, the overlapping structure-affinity/efficacy relationships and pharmacology of H_3 and H_4 receptor-targeting compounds and the differential opposing effects of some H_3 ligands in a number of experimental models [16]. Yet, the usefulness of H_3 receptor ligands in the treatment of pathophysiological states evoked by an imbalance of histaminergic interactions are currently under intense investigation, while a number of H_3 receptor ligands are on their way to the clinic (Table 1).

Despite the evidence on the contribution of postsynaptic H_1 and/or H_2 receptors in histamine-mediated transmission and in cellular mechanisms involved in arousal and cognitive functions [16], translational research has been directed towards the therapeutic potential of antagonists and inverse agonists targeting

selectively the H_3 receptor, based on a relatively complex rationale, without any proof of concept for an H_3 receptor (patho)physiological function reported so far [12].

Histamine H_4 Receptors

Following identification of the H_4 receptor some 10 years ago by several groups simultaneously, accumulating evidence points to its regulatory role in immune and inflammatory responses [14]. Contrary to the H_3 receptor predominant neuronal localization, H_4 receptors are primarily, but not exclusively, distributed in immune cells, including mast cells, eosinophils, dendritic, and T cells in peripheral tissues such as spleen, thymus, colon, blood and bone marrow, thereby eliciting chemotactic actions [cf. 14].

Importantly, however, the recently reported functional expression of H_4 receptors on human and rodent neurons (Fig. 2) highlights their implication in neuronal functions [13,38–41]. H_4 receptor expression was detected in distinct deep laminae in the human cortex [13], hippocampus, thalamus, amygdala, and spinal cord [39]. Expression of H_4 receptors has been reported in mouse thalamus, hippocampal CA4 stratum lucidum, and layer IV of the cerebral cortex, where they appear to induce hyperpolarization and promotion of outwardly rectifying currents [13], as well as in motor neuron subpopulations of the murine spinal cord [38]. In the rat, H_4 mRNA has been detected in cortex, cerebellum, brainstem, amygdala, thalamus, striatum, dorsal root ganglia, and spinal cord, while very low levels were detected in the hypothalamus and no H_4 mRNA signal in the hippocampus [39]. Recently, the H_4 receptor antagonist, JNJ-7777120, subjected intraperitoneally (i.p.) in rats reduced exploratory behavior in a dose-dependent manner [41], which may indicate a role of the H_4 receptor in motor function and/or anxiety responses, consistent with its anatomical profile. This requires further investigation in appropriately validated behavioral tests which discriminate these activities.

The human H_4 receptor gene is located in a single copy on chromosome 18q11.2 and encodes a 390 amino acid peptide belonging to the GPCR family, sharing ~35% amino acid identity with the H_3 receptor, with ~58% homology in its transmembrane regions, and only ~19% sequence similarity to the H_1 and H_2 receptors. Similarly to the H_3 receptor, the H_4 receptor is coupled to pertussis toxin-sensitive $G_{i/o}$ proteins consequently inhibiting forskolin-induced cAMP and eventually modulating the transcription of genes regulated by cAMP-responsive elements [cf. 10]. At present only two nonsignalling H_4 receptor isoforms have been identified, which may act as regulatory elements [42].

The similarities between H_3 and H_4 receptors and the overlap in their pharmacological profiles along with the high structural and pharmacological species differences displayed by the receptors and their ligands, particularly in terms of their potency, efficacy and functional selectivity [10], have resulted in frequent misinterpretations of preclinical data. Efforts are currently focused on the development of selective compounds that would provide effective pharmacological tools to assess the central and peripheral physiological role and the therapeutic potential of the H_4 receptor [12]. The high patent filing activity in this field resulted in the advancement of the H_4 receptor antagonist UR-63325 to Phase I clinical trials for respiratory diseases, while further H_4 receptor-targeting agents developed by many pharmaceutical companies and academic departments show promise for potential entry into clinical studies.

Histamine Receptors as New CNS Drug Targets

Sleep-Wake Disorders

The TM nucleus and the adjacent posterior hypothalamus are crucial for wakefulness. TM neurons, tuned via $GABA_A$ receptors activated by the GABAergic input from the ventrolateral preoptic area, project to various brain regions that control the sleep-wake cycle, such as the cortex, thalamus, preoptic and anterior hypothalamus, brainstem and forebrain, while histamine release in the prefrontal cortex is strictly correlated to waking [3,16]. The concerted action of this biogenic amine on H_1, H_2 and H_3 receptors exerts a tonic wake-selective activity pattern in the brain, which seems to be responsible for the qualitative cognitive aspects and cortical electroencephalogram activation in wakefulness, whereas orexin elicits a distinct, yet synergistic control with histamine by being involved mainly in the behavioral aspects of wakefulness [16,43]. H_1 receptor agonists and/or H_3 antagonists are promising targets for the treatment of hypersomnia, while H_1 receptor antagonists and/or H_3 agonists could be useful in controlling insomnia [44]. Despite the sedative effect of most clinically used antihistamines, some of which are marketed as sleep aids due to their daytime drowsiness side effects, they are of limited use in controlling insomnia as they have long half-lives, peripheral side effects and show inconsistent sedative patterns [45].

Selective ligands targeting the H_3 autoreceptor have been shown to be modulators of sleep phenomena and associated pathologies, such as hypersomnia, daytime somnolence and the rare but unsatisfactorily treated sleep disorder, narcolepsy [12,45]. Among the H_3 receptor antagonists that have been used in related preclinical studies, JNJ-17216498 and GSK-189254 advanced to the phase II clinical trials for the treatment of narcolepsy [18]. The cyclobutyl amide PF-03654746 is under clinical evaluation for its efficacy in improving alertness and awakeness in patients with narcolepsy-associated excessive daytime sleepiness (EDS) (Table 1). Furthermore, the H_3 receptor nonimidazole inverse agonist BF2.649 (tiprolisant) significantly reduced EDS in narcoleptic patients and currently running clinical trials are showing that it is a very promising alerting drug in Parkinson's Disease (Table 1) [46,47]. Tiprolisant passed clinical phase II studies and approved orphan drug status by the European Medicines Agency (EMEA) for the therapeutic treatment of narcolepsy.

Cognitive Disorders

Impaired cognitive functions accompany neuropsychiatric and neurodegenerative diseases such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), or schizophrenia, where most treatment strategies have focused on a single neurotransmitter system, even though disruption of multiple neurotransmitter systems is apparently involved. Histamine acting on postsynaptic H_1 and H_2 receptors functions as an excitatory neurotransmitter and plays a key role in attention and vigilance. Blockade of presynaptic H_3 autoreceptors would therefore

indirectly enhance histamine-mediated attention in cognitive disorders such as ADHD and Alzheimer's disease [48]. Besides controlling histamine release through the presynaptic H_3 autoreceptors, H_3 ligands may control the release of other transmitter systems (Fig. 1) involved in cognitive processes [16,18].

An ongoing phase II clinical trial aims to evaluate the cognitive enhancing effects of the H_3 receptor antagonist GSK-239512 in patients with mild to moderate Alzheimer's disease. In this regard, [^{3}H]GSK-189254 binding in hippocampal and cortical sections from patients with advanced Alzheimer's disease is an important observation, suggesting that H_3 expression is still prevalent even in severe late stages of the disease [48]. Other compounds, such as MK-0249 and PF-03654746 await evaluation for their effectiveness in the treatment of ADHD (Table 1).

Furthermore, tiprolisant having completed phase II trials and showing efficacy in patients suffering from antipsychotic-induced weight gain, is currently under evaluation for its cognitive enhancing effects in patients with schizophrenia and schizoaffective disorder (Table 1). In addition to the histaminergic and dopaminergic hyperactivity observed in schizophrenia, postsynaptic H_3 receptors show additive activation with striatal dopamine D_2 receptors in generating some of the disease symptoms, thus supporting the interest of H_3 receptor inverse agonists as antipsychotics, either alone or as adjunctive treatment with classical neuroleptics [49]. A very interesting feature of H_3 receptor antagonists/inverse agonists is that several of them produce cognitive enhancing effects at much lower doses than those required to elicit a robust wake enhancement [50,51]. Ideally, different compounds could be used for the treatment of sleep-wake cycle disorders or cognitive impairments.

Neuropathic Pain

Neuropathic pain is relatively common and largely resistant to treatment mainly because of the poorly understood underlying mechanisms, which include ectopic excitability of sensory neurones, sensitization of neurones in the dorsal horn of the spinal cord and, more recently, inflammatory and immune pathways [52]. Histamine as well as mast cells have been strongly implicated in the pathophysiology of neuropathic pain, while both H_3 [53] and H_4 [41] receptors seem to contribute to the underlying mechanisms. The existing data have been somewhat conflicting, mostly because of the use of experimental models with questionable relevance to the clinical situation and of the species-differences and complex pharmacology of the compounds used, such as thioperamide, which it is now known to possess both H_3 and H_4 receptor activity [12,52].

Novel selective H_3 receptor antagonists/inverse agonists, such as GSK-189254 and GSK-334429, are effective in surgically induced and virally induced rat models of neuropathic pain [54]. Histamine produces itch which might be converted into pain in neuropathic hyperalgesia [55]. Regarding H_4 receptors, the antihyperalgesic and antinociceptive effects of the H_4 receptor antagonist JNJ-7777120 have been suggested to be secondary to its antiinflammatory action [41]. JNJ-7777120 exhibited robust antinociceptive activity in persistent inflammatory (complete Freund's adjuvant-induced) pain, effectively reversed monoiodoacetate-induced osteoarthritic joint pain and produced dose-dependent antiallodynic effects in the spinal nerve ligation and sciatic nerve constriction injury models of chronic neuropathic pain, as well as in a skin-incision model of acute postoperative pain, with ED_{50} values ranging from 29–88 mg/kg i.p. [41]. Although investigations utilizing H_3 and/or H_4 receptor ligands have to be evaluated carefully, H_3 receptors in the human dorsal root ganglia and dorsal horn of the spinal cord seem to play a role in linking peripheral and central sensitization pathways [54]. Moreover, the recent demonstration of the functional expression of H_4 receptors in the brain and the strong expression in human and rodent spinal cord (Fig. 2) [13,38,39], together with the involvement of inflammatory and immune components in neuropathic pain is directing current research to the investigation of a wider contribution of the H_4 receptors in itch and pain [56].

The overall outcome of preclinical investigations led to phase I clinical trials of the highly potent histamine H_3 receptor antagonist GSK-189254 (Table 1), which demonstrated efficacy in the reduction of mechanical hyperalgesia and allodynia in the chronic constriction injury preclinical model of neuropathic pain, possibly through enhanced release of monoamines in the CNS [54].

Future Directions

Histamine and Neuroprotection

Antagonists/inverse agonists of the H_3 receptor have raised much interest in the scientific community for their potential clinical use [12], yet there are potential therapeutic applications for H_3 receptor agonists as well, that deserve consideration.

In addition to the modulation of the wake promoting effect of histamine, novel effects of H_3 receptor activation have appeared in the recent literature, including an antinociceptive role for spinal H_3 receptor activation [57]. Recently, several studies have hinted at a role of the histaminergic system and H_3 receptor in neuroprotection. The hypothesis came from Panula and collaborators who provided clear indications of the plasticity of brain histaminergic system following injury or neurotoxic insults. H_3 receptor mRNA was shown to be upregulated in the rat caudate and putamen following induction of transient global cerebral ischemia [58], or in the rat cortex following kainic acid-induced seizures [59], although with different time courses and recovery. More recently the same group elegantly demonstrated that histamine protects hippocampal neurons from damage induced by kainic acid in organotypic cocultures of hypothalamic and hippocampal tissue [60], where histamine released from hypothalamic neurons affords the neuroprotective effect of hippocampal neurons presumably by activating postsynaptic H_1 receptors. On the other hand, blockade of presumably presynaptic autoinhibitory H_3 receptors ameliorates the protective effect of histaminergic neurons [60].

In cultured murine cortical neurons, though, where no histaminergic neurons are present, and H_3 receptors are abundantly expressed, H_3 receptor stimulation activates antiapoptotic signaling cascades, such as the PI3K/Akt/GSK-3β pathway [61]. The Akt pathway has been implicated in regulating several important cellular processes, including cell plasticity and survival, proliferation and metabolism. Indeed, in cultured cortical cells, H_3 receptor agonists increase the expression of the inhibitor of

apoptosis Bcl-2 and decrease the expression of proapoptotic elements such as caspase-3, following neurotoxic insults [61]. Hence, stimulation of H_3 receptors protects cortical neurons from *N*-methyl-D-aspartate-induced neurotoxic insults and this observation may have relevance in the prevention of, for instance, ischemic neuronal damage or neurodegenerative diseases. As a matter of fact, evidence points to a key role for GSK-3β in promoting neurodegeneration [62] and it is involved in a cascade of events, such as hyperphosphorylation of tau protein, increased production of β-amyloid, local cerebral inflammatory responses that may culminate in Alzheimer's disease [63]. In this regard, binding studies showed that the expression of H_3 receptors is spared in the brain of Alzheimer's and Lewy Body Dementia patients [48, Lethbridge, Medhurst, & Chazot, unpublished]. To fully understand the impact of H_3 receptor-induced activation of anti-apoptotic pathways in the CNS, *in vivo* experiments are necessary, the more so as H_3 receptor antagonists are now viewed as potential therapeutics for schizophrenia and Alzheimer's disease (Table 1).

Multiple Sclerosis

Multiple sclerosis (MS) is the most common nontraumatic cause of neurological disability among young adults in Western Europe and North America and existing therapies are partly effective in halting ongoing inflammatory tissue damage and clinical progression. MS pathogenesis is complex and probably heterogeneous among patients, suggesting that combination therapy strategies that target a range of disease mechanisms might be more effective than medications used as monotherapy [64].

Increasing evidence indicates that histamine is also involved in the pathophysiology of MS and its most widely used animal model, experimental autoimmune encephalomyelitis (EAE) [27,65]. The interest in histaminergic compounds for the treatment of MS stems mostly from preclinical studies although in a small pilot study as well, a cohort of MS patients treated with the H_1 receptor antagonist hydroxyzine showed signs of neurological amelioration [66]. Recent evidence indicates a role for H_1 receptors in autoimmune demyelination and extensive involvement of elements of the immune response associated with allergy in EAE [67]. H_2 receptors also seem to regulate in part encephalitogenic T cell responses and EAE susceptibility, as mice lacking H_2 receptors present less severe acute, early-phase of the disease [68]. Moreover, H_3 receptor knock-out mice developed a more severe form of EAE than their wild type littermates, an effect that the authors attributed to altered blood–brain barrier permeability [68]. Considering the immunoregulatory role of the H_4 receptor in inflammatory responses and the compelling evidence associating H_4 receptors with atopic and autoimmune disorders [14,56], it is intriguing to speculate an H_4 receptor role in EAE and the possible attenuation of the immune response and amelioration of the neurological signs following blockade of the H_4 receptor, a hypothesis that is currently under investigation.

Concluding Remarks

The identification of the histamine H_3 and H_4 receptors is pivotal in refining our understanding of the pharmacology and the therapeutic potential of this biogenic amine. Classically established as a "peripherally" important mediator of inflammation, histamine is now accepted to play a role in neurotransmission (Fig. 1) and to provide new CNS drug targets, similarly to the other biogenic amine systems exploited by neuropharmacology, including noradrenalin, dopamine and serotonin, which are major targets for medication commonly used in neuropsychiatry. Histamine exerts its central effects through H_1, H_2, and H_3 receptors. The latter, whether presynaptic autoreceptors that inhibit the synthesis and release of histamine in the histaminergic neurones or postsynaptic heteroreceptors, are predominately distributed in the CNS and seem to be a suitable target for CNS drug development. Furthermore, the recent intriguing observation of the functional expression in enteric and central neurons of the predominantly peripheral H_4 receptor (Fig. 2), which is undergoing rigorous characterization at present, adds further complexity to the role of histamine in the CNS. Thus, a potential interaction of the histamine receptors in the overall brain (patho)physiolology cannot be excluded at present.

Although important questions regarding the (patho)physiology of the central histaminergic system remain to be answered, H_3 receptors have gained widespread attention by various academic and industrial laboratories for the development of ligands currently undergoing extensive preclinical pharmacological profiling for clinical candidate selection in a plethora of experimental models of human diseases. A number of antagonists and inverse agonists have advanced into clinical assessment (Table 1) for their safety and effectiveness in disorders of the sleep-wake cycle such as narcolepsy, in neuropathic pain and as cognition enhancers in ADHD, schizophrenia, Alzheimer's, and Parkinson's disease, the results of these clinical trials being eagerly awaited. Moreover, the increasing evidence for a role of the histaminergic system in neuroprotection and in the pathophysiology of MS has started to motivate vigorous related investigations in order to progress our understanding of the properties of histamine and its receptors, and to meet the challenge of identifying potential new drug targets in the neuropsychiatric and neuroimmunological arenas.

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Conflict of Interest

The authors have no conflict of interest.

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