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# HISTAMINE NEURONAL SYSTEM AS THERAPEUTIC TARGET FOR THE TREATMENT OF COGNITIVE DISORDERS

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## HISTAMINE IS A NEUROTRANSMITTER

The first indication of the functional importance of histamine in the CNS can be traced back to the 1930's, when it was observed that centrally penetrating histamine H<sub>1</sub> antagonists had marked sedative properties. Yet, no attention was given to histamine receptors as sites of action for these unwanted effects (1). Indeed, histamine role as a neurotransmitter has been neglected for many years, in spite of early reports of its presence in the brain (2), and suggestions that this amine has central functions (3). The delay in searching for a histaminergic neuronal system, compared to the exploration of other aminergic neurotransmitter systems, may rest on the methods available for their visualization. The distribution of the catecholaminergic and serotonergic neurons in the brain became known using a fluorescent immunohistochemical analysis with o-phthalaldehyde as a tracer (4). However, the same method was not suitable for visualizing histamine because of a strong interference with the ubiquitous spermidine (5). The first direct evidence of the existence of histaminergic neurons came only in the 1980's, with the development of immunohistochemistry using antibodies against histamine (6) and histidine decarboxylase (7). All histaminergic neurons are localized in the tuberomammillary nucleus (TMN) of the posterior hypothalamus (6, 7), that is also location of histidine decarboxylase immunoreactivity (8), an essential determinant of brain histamine levels (9, 10). They project to almost all regions of the central nervous system (11) mostly unmyelinated fibers that, with the exception of the mesencephalic trigeminal nucleus (12), do not form synaptic contacts, but present diffuse varicosities containing synaptic vesicles (13, 14). This peculiarity suggests that histamine may act as a local hormone affecting not only neuronal, but also glial activity and blood vessel tone (15). Consistently, cultured astrocytes from rat cerebral cortex display histamine receptors identical to those present on neuronal cells (16, 17). This morphological feature, a

compact cell group with widely distributed fibers, resembles that of other biogenic amines systems, such as norepinephrine or serotonin, thus suggesting that histaminergic neurons as well may regulate several central functions.

## **HISTAMINE RECEPTORS AS THERAPEUTIC DRUG TARGETS**

Histamine exerts its effect interacting with specific receptors, H<sub>1</sub>R (18), H<sub>2</sub>R (19), H<sub>3</sub>R (20) H<sub>4</sub>R (21), and with the polyamine-binding site on the NMDA receptor complex (22). All four histaminergic receptor subtypes belong to the rhodopsin-like family of G protein-coupled receptors (GPCR) (23, 24), and are functionally expressed on neurons in the mammalian central nervous system (5, 25). The first two members of the histamine receptor family, H<sub>1</sub>R and H<sub>2</sub>R are well established drug targets, and antagonists of these receptors have been successful as blockbuster drugs for treating allergic conditions and gastric ulcers. Whereas at present H<sub>4</sub>R is still waiting for a better functional characterization, the discovery of the H<sub>3</sub>R by Jean-Charles Schwartz and his group in Paris has been a real breakthrough in histamine research (20). This receptor is largely confined to the nervous system (26), where it acts as a presynaptic autoreceptor that restricts histamine release as well as synthesis both *in vitro* (20), and *in vivo* (27-30). The H<sub>3</sub>R is located also on histaminergic somata where it provides a tonic inhibition of firing (31). Moreover, the presence of the H<sub>3</sub>R is not restricted to histaminergic neurons (32-34). Accordingly, H<sub>3</sub>Rs act also as heteroreceptors modulating the release of other neurotransmitters, including ACh (35, 36), dopamine (37), noradrenaline (38) and serotonin (39, 40) from brain regions crucial for the maintenance of alertness or the storage of information (1). Network analyses of the brain and its dysfunction suggest that agents with multiple and complementary modes of action are more likely to show broad-based efficacy against core and comorbid symptoms. Thus, the regulatory role in the release

of histamine and other neurotransmitters makes the H<sub>3</sub>R an attractive target for therapies of CNS disorders, and H<sub>3</sub>R ligands are good therapeutic candidates for their simultaneous exploitation of multiple neuronal systems. Consistently with the widespread distribution throughout the entire central nervous system of histaminergic fibers (41, 42), brain histamine is, directly or indirectly, involved in a variety of basic homeostatic and higher brain functions, such as sleep-wake cycle, appetite, nociception, cognition and emotion (1, 5). H<sub>3</sub>R antagonists/inverse agonists have been shown to increase wakefulness, improve cognitive performances and reduce body weight in animal models (5). Such findings hint at the potential use of these compounds for the treatment of Alzheimer's Disease and other dementias, ADHD, cognitive deficits in schizophrenia, obesity and sleep disorders (43-46). Thus, it is not surprising that much effort is focused on the development of clinically suitable H<sub>3</sub>R antagonists/inverse agonists by academic and industrial laboratories (45-47). As a result, more and more H<sub>3</sub>R antagonists/inverse agonists (ABT-239, [4-(2-{2-[(2R)-2-methylpyrrolidinyl]ethyl}-benzofuran-5-yl)benzotrile; BF2.649, 1-{3-[3-(4-Chlorophenyl)propoxy]propyl}piperidine, hydrochloride; GSK189254, 6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-N-methyl-3-pyridinecarboxamide hydrochloride; JNJ-10181457, 4-[3-(4-Piperidin-1-yl-but-1-ynyl)-benzyl]-morpholine; MK-0249, not disclosed structure; PF-03654746, not disclosed structure) progress through the clinic for a variety of conditions, including Attention-deficit Hyperactivity Disorder (ADHD), Cognitive disorders, Hyperalgesia, Narcolepsy and Schizophrenia (46).

### CHARACTERISTICS OF THE H<sub>3</sub>R

H<sub>3</sub>R is largely confined to the nervous system and the highest levels were found in the cerebral cortex, hippocampus, basal ganglia, and hypothalamus (33, 34). This receptor has multiple splice variants. Not all isoforms appear to

be functional and some of them might regulate functional isoforms by associating with them (48). H<sub>3</sub>R<sub>s</sub> are members of the seven transmembrane receptor superfamily (49) and couple to G<sub>i/o</sub> proteins (50). Their stimulation restricted the influx of calcium ions (51), inhibited adenylate cyclase (49), and increased extracellular signal-related kinase (ERK) phosphorylation in receptor-transfected cells (52). All histaminergic receptors displayed a high degree of constitutive (agonist-independent) activity, that occurred in human, rat and mouse recombinant receptors expressed at physiological concentrations (53-56). Noteworthy, constitutive activity of native H<sub>3</sub>R<sub>s</sub> seems one of the highest among GPCRs in the brain (57). Constitutively active H<sub>3</sub>R<sub>s</sub> presumably regulate the release of neuronal histamine (55), therefore several H<sub>3</sub>R antagonists (e.g.: clobenpropit, thioperamide and ciproxifan) that block constitutive activity are being reclassified as inverse agonists, a concept that may have clinical relevance. Indeed, either inverse agonists or neutral antagonists may be favorable for different therapeutic applications.

### **THERAPEUTIC POTENTIALS OF H<sub>3</sub>R ANTAGONISTS/INVERSE AGONISTS IN COGNITIVE AND EMOTIONAL DISORDERS**

Considerable interest was raised by reports that pharmacological blockade of H<sub>3</sub>R<sub>s</sub> exerted procognitive effects in a variety of animal tasks analyzing different types of memory. In the social memory (58, 59), the five-trial inhibitory avoidance task (60, 61), and the five-choice, serial reaction time test (62), rats treated with H<sub>3</sub>R antagonists/inverse agonists performed better than controls. Further studies indicated that both imidazole and non-imidazole H<sub>3</sub>R antagonists/inverse agonists exerted procognitive effects also in cognitively impaired animals: as observed in senescence-accelerated mice or scopolamine-impaired rats challenged in a passive-avoidance response (63, 64), scopolamine-impaired rats tested in the object recognition (43, 64, 65)

or the elevated plus-maze paradigm (66), and MK-801-treated rats evaluated in the radial maze (67). Administration of non-imidazole H<sub>3</sub>R antagonists/inverse agonists, A-304121 or A-317920 improved cognitive performances also in spontaneously hypertensive rat pups, which were normotensive during early development, but exhibited many cognitive impairments (60, 61). Certainly, such a model is clinically very relevant, as deficits are genetic in origin and do not require pharmacological or surgical intervention. Although another report provided some contrasting data, as H<sub>3</sub>R antagonists/inverse agonists impaired object recognition in wild-type and *ApoE*<sup>-/-</sup> mice (68), these findings may be relevant to predict the potential of H<sub>3</sub>R antagonists/inverse agonists in ameliorating cognitive dysfunctions in humans(61). In this regard, it is important the demonstration that [3H]GSK189254 labeled H<sub>3</sub>R<sub>s</sub> in hippocampal and cortical sections from patients with advanced AD (69), suggesting the persistence of H<sub>3</sub>R<sub>s</sub> even in severe AD.

If cognitive deficits are related to reduced availability of acetylcholine (ACh) in the synaptic cleft (70), increase of ACh release in the prefrontal cortex exerted by H<sub>3</sub>R antagonists/inverse agonists could account for the procognitive effects produced by these compounds, at least in short term memory paradigms with important cortical cholinergic components, such as object recognition (71) and a passive avoidance response (72). Indeed, H<sub>3</sub>R ligands modulate cortical ACh release in a bimodal fashion, and modify the expression of memories accordingly. Stimulation of cortical H<sub>3</sub>R<sub>s</sub> inhibited local ACh release, and impaired object recognition and a passive avoidance response (36). Conversely, TMN perfusion with GSK189254, a non-imidazole H<sub>3</sub>R antagonists/inverse agonists, increased significantly the release of cortical ACh in freely moving rats, and counteracted amnesic effects produced by scopolamine administration in rats as measured in object recognition (65). Cortical ACh increase can be a consequence of the

augmentation of histamine release in the nucleus basalis magnocellularis (NBM) elicited by intra-TMN administration of GSK189254 (65). Indeed, histamine, by activating H<sub>1</sub> receptors, depolarized the cell membrane and increased the tonic firing of NBM cholinergic neurons (73), that provide all cholinergic innervation to the cortex (74). These findings are in keeping with the report that perfusion of the NBM with H<sub>3</sub>R antagonists/inverse agonists increased cortical ACh release (75). H<sub>3</sub>R antagonists/inverse agonists also augmented NBM histamine release by blocking local H<sub>3</sub>-autoreceptors (65, 76). A comparable enhancement of cortical ACh was observed also in response to systemic administration of several non-imidazole H<sub>3</sub>R antagonists/inverse agonists, such as ABT-239 (59), BF2.649 (77), or GSK189254 (78). Neuronal alterations associated to cognitive deficits are not restricted to the cholinergic systems as many neurotransmitter systems, including dopamine, contribute to specific aspects of cognition. Therefore, it is important to point out that systemic administration of ABT-239 (59), or BF2.649 (77) increased also the release of cortical dopamine. H<sub>3</sub>R antagonists/inverse agonists though failed to increase dopamine release from other regions such as the striatum (59) or the nucleus accumbens (65), and these observations may provide the rational basis for clinical indication in disorders like schizophrenia or ADHD.

Interactions between the histaminergic and cholinergic systems serve as one of the physiological correlates for learning and remembering, however, H<sub>3</sub>Rs modulate ACh release with modalities that differ according to regional architectural constraints, to their role as auto- or hetero-receptors, and to the distinct actions that histamine exerts by activating different receptor subtypes. Noteworthy, basolateral amygdala (BLA) perfusion with H<sub>3</sub>R agonists increases, whereas with H<sub>3</sub>R antagonists/inverse agonists decreases ACh release from the BLA (79, 80). These drugs impacted presumably on inhibitory H<sub>3</sub>-autoreceptors, as in the BLA H<sub>3</sub>R receptor binding was strictly



associated with the presence of histaminergic fibers (81). Consistently, BLA perfusion with H<sub>3</sub>R antagonists/inverse agonists increased endogenous histamine release (82), which, in turn activated postsynaptic H<sub>2</sub>R<sub>s</sub>, and inhibited ACh release (79). The BLA receives the most abundant histaminergic innervation in the brain (83), and displays both high H<sub>2</sub>R binding and its gene transcripts (84). Crucial neural changes mediating emotional memory occur in the BLA (85, 86). Emotional memory may be assessed with contextual fear conditioning in which experimental animals learn to associate a mild electrical foot-shock with the environment where they receive the punishment. A critical event for aversive memory consolidation is the activation of muscarinic receptors within the BLA (79, 80, 87). In this regard, it is relevant that BLA perfusion with H<sub>3</sub>R antagonists/inverse agonists impaired (79), whereas with H<sub>3</sub>R agonists ameliorated expression of this form of associative memory (80). These results contrast with the findings in the cortex. Nevertheless, since BLA is engaged in the development of mood disorders associated with extreme emotional traumas, the use of H<sub>3</sub>R antagonists/inverse agonists that weaken traumatic memories may be proposed to alleviate disorders such as post-traumatic stress syndrome (PTSD), panic attacks, specific phobias and generalized anxiety.

Brain histamine affect emotional memory also eliciting ERK2 phosphorylation in hippocampal CA3 pyramidal cells, an event that is crucial for the consolidation of contextual fear memory (88).

### **AROUSAL ELICITED BY H<sub>3</sub>R ANTAGONISTS/INVERSE AGONISTS AND ITS CONTRIBUTION TO PROCOGNITIVE EFFECTS**

Cognition is a complex phenomenon involving the integration of multiple neurological activities among which arousal is crucial (89, 90). Histamine is, along with orexin, one of the major wake-promoting neurotransmitters in the central nervous system (91), as histidine decarboxylase knock-out mice that

lack histamine, are unable to remain awake when high vigilance is required (92). Also narcoleptic dogs show histamine deficiency (93). It is known that histaminergic neurons fire at higher frequency during wakefulness than during sleep (94). Moreover, histamine is responsible for cortical EEG desynchronization (91), a salient sign of wakefulness (1, 95). Brain histamine elicits cortical activation directly, through excitatory interactions with cholinergic corticopetal neurons originating from the substantia innominata (96) and the nucleus basalis magnocellularis (75), and indirectly, as it activates, through stimulation of cholinergic neurons in the mesopontine tegmentum, thalamo- and hypothalamo-cortical circuitries (97). H<sub>3</sub>R blockade by local perfusion of thioperamide into the TMN increased the time spent in wakefulness along with the release of TMN histamine in freely moving rats (76), thus suggesting that they, by increasing arousal, may enhance attention and improve cognitive performances. However, several H<sub>3</sub>R antagonists/inverse agonists produced cognitive enhancing effects at much lower doses than those required to elicit a robust wake enhancement (59, 61). For example, ABT-239 produced no detectable change in slow-wave EEG at 30 mg/kg, whereas it was effective in social recognition at 0.01 mg/kg (59). Consistently, for ciproxifan, thioperamide or GSK189254, only a relatively low level of cumulative wake activity was linearly correlated with up to 80% of the receptor occupancy, and an abrupt break from linearity along with a robust increase of waking activity was observed at doses that produced greater than 80% occupancy (98). High or low levels of H<sub>3</sub>R occupancy may express activities mechanistically different, and H<sub>3</sub>R antagonists/inverse agonists procognitive actions may not relate to increased arousal. Thus, lower dosage might be used to address H<sub>3</sub>R antagonists/inverse agonists actions specifically towards cognition. This is an important issue, since nocturnal sleep should ideally not be disturbed by drug therapies. Nevertheless, at least at higher dosage, this class of drugs

constitutes a novel effective treatment of narcolepsy and excessive daytime sleepiness (EDS), and this contention is supported by both preclinical and clinical data. Indeed, acute administration of GSK189254 reduced narcoleptic episodes in orexin knock out mice (99). Moreover, in a pilot single-blind clinical trial on 22 patients diagnosed with narcolepsy receiving a placebo for a week, followed by tiprolisant (BF2.649) for another week, the Epworth Sleepiness Scale (ESS) score was reduced from a baseline value of 17.6 by 1.0 with the placebo ( $p>0.05$ ) and 5.9 with tiprolisant ( $p<0.001$ ) (100). Excessive daytime sleep, unaffected under placebo, was nearly suppressed on the last days of tiprolisant dosing (100).

### **H<sub>3</sub>Rs AND NEUROPROTECTION**

Much of the recent interest in developing new ligands of the H<sub>3</sub>R stems from the potential use of H<sub>3</sub>R antagonists in controlling feeding behaviour, disorders of the sleep-wake cycle and cognitive impairments associated with Alzheimer's or Parkinson's disease (reviewed in (101)). However, there are potential therapeutic applications for H<sub>3</sub>R agonists as well. H<sub>3</sub>R activation in the CNS results in lower hypothalamic histamine release and H<sub>3</sub>R agonist may be used against insomnia (102). Also, Hough and co-workers have revealed an antinociceptive role for spinal histamine H<sub>3</sub>R (103). In the past years, several studies have hinted at a role of the histaminergic and H<sub>3</sub>R in neuroprotection. The first clear indication of how plastic the brain histaminergic system is following injury, was provided by Panula and collaborators. They showed that H<sub>3</sub>R mRNA is up-regulated in the rat caudate and putamen following induction of transient global cerebral ischemia (104), or in the rat cortex following kainic acid induced seizures (105), although with different time courses and recovery. A more recent, paper published by the same group elegantly demonstrated that histamine protects hippocampal neurons from damage induced by kainic acid in

organotypic co-cultures of hypothalamic and hippocampal tissue (106). The hypothalamic histaminergic innervation of hippocampal neurons affords the neuroprotective effect and the blockade of, presumably presynaptic autoinhibitory, H<sub>3</sub>R ameliorates the protective effect histaminergic neurons. We recently showed that H<sub>3</sub>R agonists activate anti-apoptotic pathways such as the PI3K/Akt/GSK-3 $\beta$  pathway (107). The Akt pathway has been implicated in regulating several important cellular processes, including cell plasticity and survival, proliferation and metabolism. Akt promotes neuronal cell survival and opposes apoptosis by a variety of routes, e.g. modulating inhibitors of apoptosis such as Bcl-2 and Bcl-x (Song et al. 2001). Indeed, H<sub>3</sub>R agonists in our model increase the expression of Bcl-2, and decreases the expression of pro-apoptotic elements such as caspase-3 following neurotoxic insults in cultured murine cortical neurons (107). Hence, stimulation of H<sub>3</sub>R protects cortical neurons from NMDA-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, schizophrenic patients have impaired Akt/GSK-3 $\beta$  signalling (108) and evidence points to a key role for GSK-3 $\beta$  in promoting neurodegeneration (109). GSK3 is involved in a cascade of events, such as hyperphosphorylation of tau protein, increased production of  $\beta$ -amyloid, local cerebral inflammatory responses that may culminate in Alzheimer's disease (110). In this regard, binding studies showed that the expression of H<sub>3</sub>R is spared in the brain of Alzheimer's patients (78). To fully understand the impact of H<sub>3</sub>R-induced activation of antiapoptotic pathways in the CNS, *in vivo* experiments are necessary, the more so as H<sub>3</sub>R antagonists are now viewed as potential therapeutics for schizophrenia (77) and Alzheimer's disease (78).

## HETEROGENEITY OF HISTAMINERGIC NEURONS

In a comparable architecture to noradrenergic, dopaminergic, and serotonergic systems (111, 112), somata of histaminergic neurons are restricted to discrete cell clusters in the hypothalamic TMN, and send their axons to innervate nearly the entire central nervous system (6, 7). Catecholaminergic and serotonergic nuclei are comprised of distinct compartments with respect to projection fields, as distinct sets of axons innervating separate brain regions originate from separate subgroups of noradrenergic (A1-A7), dopaminergic (A8-A17), and serotonergic (B1-B9) neurons (111, 112). This does not seem to be the case for the histaminergic system, as retrograde tracers injected into different CNS regions labeled histaminergic somata scattered throughout the TMN without a strict topographical pattern (8, 11, 113). Noradrenergic, dopaminergic, and serotonergic patterns imply independent functions of sets of neurons according to their origin and terminal projections. On the contrary, the morphological feature of the histaminergic system is consistent with the hypothesis of a single regulatory network for whole-brain activity, which modulates general states of metabolism and consciousness, rather than processing specific functions (15). However, very recently direct evidence demonstrated that histaminergic neurons as well are organized into functionally distinct circuits impinging on different brain regions, and displaying selective control mechanisms. Using the double-probe microdialysis technique in freely-moving rats it was observed that histaminergic neurons established distinct pathways related to independent functions according to their terminal projections, and to their sensitivity to H<sub>3</sub>R antagonists/inverse agonists or GABA<sub>A</sub>-receptor antagonists (65, 76). GABA<sub>A</sub>-R activation inhibits directly histaminergic cell firing rate (114, 115), whereas inhibition increases significantly TMN histamine release (116). Depending on GABA<sub>A</sub>-R subunit expressions, histaminergic neurons displayed different sensitivity to GABA (117, 118). This may account for the functional heterogeneity of GABAergic

responses displayed by histaminergic neurons following stimulation of the diagonal band of Broca, the antero-lateral hypothalamus, or the lateral preoptic area (114). The finding that Intra-hypothalamic perfusion of bicuculline increased histamine release from the TMN, the nucleus accumbens and cortex, but not from the striatum (76), indicates that sensitivity to bicuculline relates to TMN neurons heterogeneity also with respect to projection fields.

Application of imidazole or non imidazole H<sub>3</sub>R antagonists/inverse agonists locally into the TMN, significantly increased histamine release from the TMN, the prefrontal cortex and the NBM, but not from the striatum or nucleus accumbens (65, 76). These findings indicate that histamine neurons projecting to the dorsal striatum and nucleus accumbens were insensitive to blockade of H<sub>3</sub>R (65, 76). Spatial segregation due to probe localization does not explain why histaminergic neurons projecting to the striatum or nucleus accumbens do not respond to H<sub>3</sub>R antagonists/inverse agonists. Infact, bicuculline administered into the TMN augmented significantly histamine release from the nucleus accumbens (76), and TMN perfusion with cannabinoid1 receptor agonists increased histamine from the dorsal striatum (116), confirming the existence of histaminergic afferents to the striatum. Furthermore, retrograde tracing with dye injections into the striatum or prefrontal cortex labeled most histaminergic somata within the same area, the medial part of the ventral TMN [Kohler, 1985 #2243]. This proximity suggests that the compounds administered through the microdialysis probe affected, indiscriminately, histaminergic cells projecting to the striatum and prefrontal cortex. Interestingly, previous studies showed that following GSK189254 administration, activation of c-fos occurred in cortical areas and the TMN, but not in striatum (78). Moreover, local perfusion of the striatum with H<sub>3</sub>R antagonists/inverse agonists did not alter spontaneous histamine release (65, 76), suggesting that the entire somatodendritic domain of

histaminergic neurons projecting to this region were insensitive to H<sub>3</sub>R blockade. Since the magnitude of neuronal responses to extracellular signals might depend also on different receptor number at the membrane, it is important to underline that in the TMN, some HDC-positive cells displayed very low levels of H<sub>3</sub>R immunoreactivity (76), although no evidence demonstrates that these cells are the ones innervating the nucleus accumbens or striatum. On the other hand, histamine increases in the prefrontal cortex and NBM were likely due to discharge potentiation of histamine neurons sending afferents to these regions, in analogy to TMN perfusion with prostaglandin-E<sub>2</sub> (119), orexin-A (120), or endocannabinoids (116).

These observations suggest that the histaminergic system is organized into distinct circuits modulated by selective mechanisms. This could imply independent functions of subsets of histaminergic neurons according to their respective origin and terminal projections.

## **CONCLUDING REMARKS**

A wide variety of studies agree that the neuronal histaminergic system regulates some forms of cognition, and, inevitably, reports that pharmacological blockade of central H<sub>3</sub>R<sub>s</sub> exerted procognitive activity in several cognitive tasks has raised considerable interest. The molecular pharmacology is uncovering the extraordinary complexity of the H<sub>3</sub>R: it shows functional constitutive activity, polymorphisms in humans and rodents with a differential distribution of splice variants in the central nervous system, and potential coupling to different intracellular signal-transduction mechanisms (1, 5). Thus, it will be a great challenge in the years to come to develop ever more selective agonists, inverse agonists, pure antagonists of the H<sub>3</sub>R, as well as ligands for its various isoforms. All histaminergic neurons are believed to express H<sub>3</sub>R<sub>s</sub>, and response to H<sub>3</sub>R ligands is a criterion for

their identification *in vitro*. Contrary to this general assumption, it has been recently reported that histamine neurons projecting to the striatum and nucleus accumbens are insensitive to thioperamide, an H<sub>3</sub>R antagonist (65, 76), thus suggesting that histamine neurons are more functionally heterogeneous than previously thought (15). Although further studies are required to understand the full implications of such functional heterogeneity of histaminergic neurons, the possibility that H<sub>3</sub>R control only some of those functions implies that H<sub>3</sub>R-directed therapies may achieve selective effects with minimal side effects, and this may increase the interest for this class of drugs.

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