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REVIEW ARTICLE

Changes in Histaminergic System in Neuropsychiatric Disorders and the Potential Treatment Consequences

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Abstract: In contrast to that of other monoamine neurotransmitters, the association of the histaminergic system with neuropsychiatric disorders is not well documented. In the last two decades, several clinical studies involved in the development of drugs targeting the histaminergic system have been reported. These include the H_3R-antagonist/inverse agonist, pitolisant, used for the treatment of excessive sleepiness in narcolepsy, and the H_1R antagonist, doxepin, used to alleviate symptoms of insomnia. The current review summarizes reports from animal models, including genetic and neuroimaging studies, as well as human brain samples and cerebrospinal fluid measurements from clinical trials, on the possible role of the histaminergic system in neuropsychiatric disorders. These studies will potentially pave the way for novel histamine-related therapeutic strategies.

Keywords: Histamine, histidine decarboxylase, histamine receptors, histamine N-methyltransferase, Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, schizophrenia and intellectual disability.

1. INTRODUCTION

In human neuropsychiatric disorders, effective treatments have been developed based generally upon changes in neurotransmitter systems affected by the disorder. For instance, dopaminergic neurons in the substantia nigra are largely lost in Parkinson's disease patients (PD) [1-3], and L-dopa (the precursor of dopamine) was developed as the first-line treatment. In addition, a genetic study showed that serotonin transporter genes are highly associated with depression and anxiety disorders [4], and patients are successfully treated with selective serotonin reuptake inhibitors (SSRIs).

A number of physiological functions are modulated by the neuronal histaminergic system. These include the sleep-wake cycle, sensory and motor functions, cognition and attention, all of which are affected in neuropsychiatric disorders. Significant clinical progress has been made in the use of the H_3R-antagonist/inverse agonist for the treatment of excessive sleepiness of narcolepsy [5, 6]. It is time to systematically review the pathophysiology of the histamine system in order to implement novel therapeutic strategies for the treatment of neuropsychiatric disorders. In the present review, we summarize findings from DNA, RNA and protein expression studies, neuroimaging reports, cerebral spinal fluid (CSF) measurements and recent clinical trials to discuss histamine receptors and key enzymes of histamine synthesis and metabolism, and their possible involvement in neuropsychiatric disorders.

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2. HISTAMINE SYNTHESIS, METABOLISM AND RECEPTORS IN THE CENTRAL NERVOUS SYSTEM

Neuronal histamine is produced in the hypothalamic tuberomamillary nucleus (TMN) [7, 8], where histidine decarboxylase (HDC), involved in the synthesis of histamine, is the key enzyme (Fig. **1**). HDC immunoreactivity is often used as a marker of histamine neurons. The TMN innervates several brain areas, including the hypothalamus, basal ganglia, prefrontal cortex, and hippocampus. Histamine is inactivated by conversion to tele-methylhistamine (t-MeHA) by the enzyme histamine N-methyltransferase (HMT) [9-11] (Fig. **2**). There are 4 types of G protein-coupled histamine receptors widely expressed in the brain ($H_{1\text{-}4}$R) [9-11]. The H_3R is also an auto receptor located pre-synaptic to modulate the release of histamine, glutamate, GABA, acetylcholine, norepinephrine and serotonin.

3. HDC

3.1. Circadian Rhythmicity of HDC Expressing Neurons

Since Dahlstrom and Fuxe's discovery that monoaminergic cells are segregated in discrete populations [12], it has been assumed that the brain contains a fixed number of each type of monoaminergic neuron. There are about 64000 histaminergic neurons in the TMN [13]. However, the number of HDC expressing neurons fluctuates according to the time of day. Diurnal fluctuations of HDC-mRNA and protein levels have been reported in rodents and humans [14, 15]. In mice, the number of HDC immunoreactive neurons was 34% greater in the active phase than in the rest phase [16]. Some neurons may produce HDC at levels below the detection threshold of immunohistochemistry, becoming detectable only during

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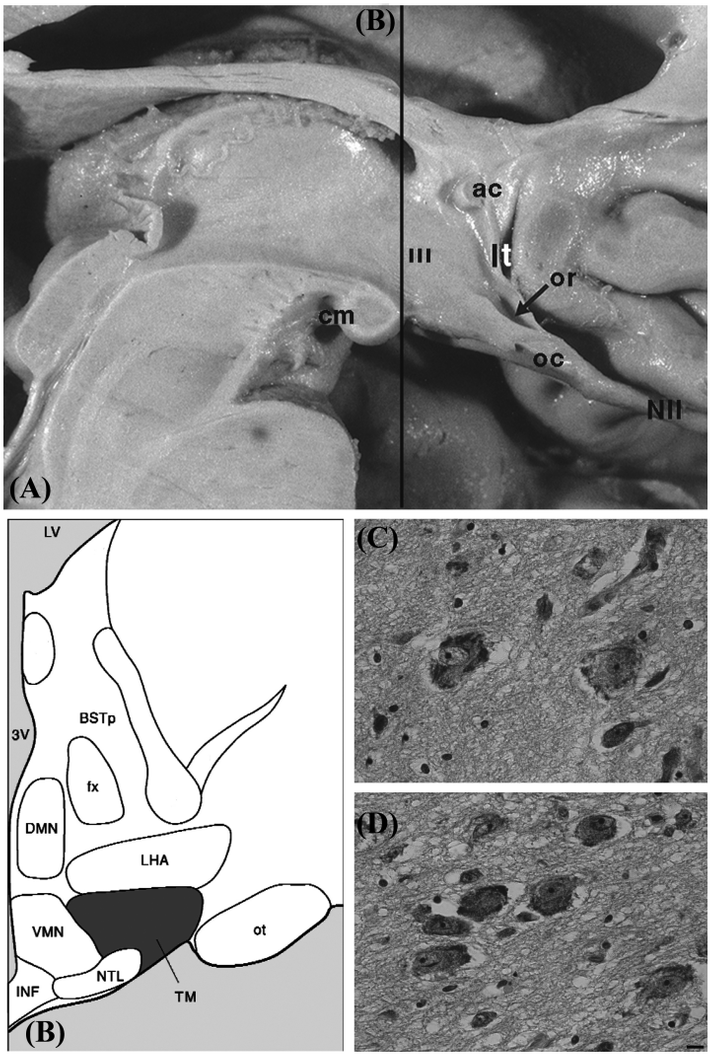

Fig. (1). The tuberomamillary nucleus (A). Medial surface of the human hypothalamus. Line **b** indicating the layer for Figure (**B**). Abbreviations: ac: anterior commissure, cm: corpus mamillare, lt: lamina terminalis, NII: optic nerve, oc: optic chiasm, or: optic recess, III: third ventricle. **B:** the human hypothalamus in representative coronal cuts with the tuberomamillary nucleus highlighted (Adapted from [100]; Fig. 2.) Abbreviations: BSTp: bed nucleus of the stria terminalis posterior, DMN: the dorsomedial hypothalamic nucleus, ot: optic tract, oc: optic chiasma, fx: fornix, INF: infundibular nucleus, LHA: Lateral hypothalamus, LV: lateral ventricle, NTL: Lateral tuberal nucleus, TM: tuberomamillary nucleus, VMN: ventromedial hypothalamic nucleus, 3V: third ventricle. (**C** and **D**). examples of Nissl staining of TM nucleus neurons w ith typical neuron profiles, scale bar = 5μm ([101] with permission). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

the active phase. Similarly, histidine decarboxylase-mRNA expression was 37% higher in humans with a clock time of death (the time of the day the case passed away) during the daytime than in those with a clock time of death at night [14]. However, the diurnal HDC-mRNA fluctuations were lost in some patients with Alzheimer's disease (AD), PD, preclinical PD, and Huntington's disease [17]. The sleep-wake disturbance of these diseases may thus, at least in part, be caused by the attenuated increase in arousal-induced histamine levels [17, 18]. Furthermore, HDC-mRNA expression and protein levels were altered in mice with a knockdown of *BMAL1*, a key clock gene, in TMN neurons. These mice also showed altered sleep architecture [15]. The neuronal histamine modulated the output pathway of the circadian system. In the HDC knockout mice, the 24-hour profiles of clock genes in the suprachiasmatic nucleus were intact, whereas the rhythms of mPer-mRNA were altered in other brain areas, such as the cortex and striatum [19]. Conditional knockout CRISPR-Cas 9 mice with neuron-specific deletion of HDC also showed a reduction in circadian activity [20]. Together these findings support the role of HDC in maintaining normal circadian rhythmicity.

3.2. Unaltered HDC Expression in both PD and AD

In PD pathology, Lewy-bodies start accumulating in the TMN at the preclinical stage [21]. However, the HDC-mRNA levels, the number of histaminergic neurons and the enzymatic activity of HDC were found to be stable in PD patients [22-24]. Furthermore, CSF levels of the main metabolite of histamine, t-MeHA, also remained unchanged in PD patients [25]. Despite the significant loss of histaminergic neurons in AD,

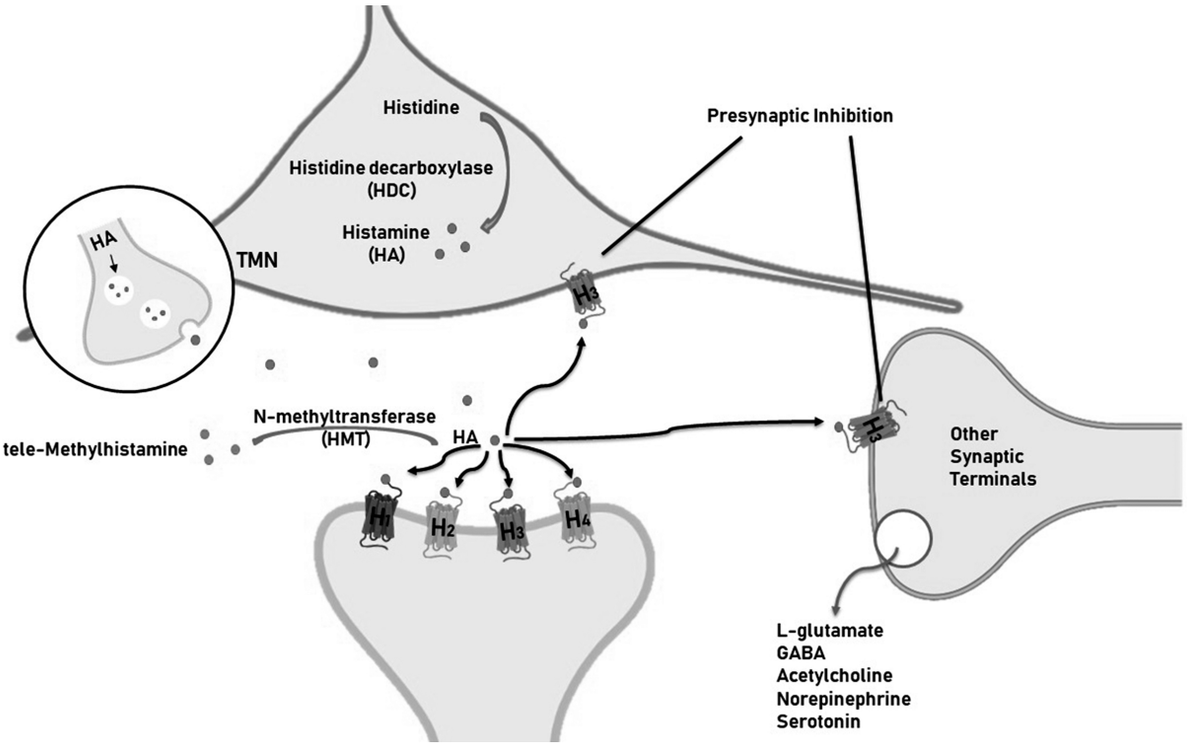

Fig. (2). Schematic illustration of histamine synthesis, metabolism and receptors in brain. Histamine is synthesized by the enzyme, histidine decarboxylase (HDC) in the tuberomamillary nucleus (TMN). The enzyme histamine N-methyltransferase (HMT) inactivates histamine. There are 4 types of histamine receptors ($H_{1\text{-}4}R$). The H_3R is also an auto receptor located pre-synaptic to modulate the release of histamine, glutamate, GABA, acetylcholine, norepinephrine and serotonin. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

expression of HDC-mRNA remained unaltered in the TMN [26].

3.3. Increased HDC Immunoreactivity in Narcolepsy Type 1 Patients

The loss of up to 90% of the hypocretin (orexin) neurons in the hypothalamus is a major cause of narcolepsy with cataplexy (narcolepsy type 1) [27, 28]. Narcolepsy is a disabling neurological disease characterized by symptoms of excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep [29]. The major clinical symptoms are also exhibited in animal models with disrupted hypocretin pathways [30-32]. The hypothalamic hypocretinergic neurons project to the histaminergic neurons in the TMN. In 2013, two research groups independently observed that HDC immunoreactivity was greatly increased in the TMN of narcoleptic patients [33, 34]. In contrast to the increased number of HDC-positive neurons in humans, decreased [35, 36] or unchanged [37] histamine levels were observed in the lumbar CSF of narcolepsy type 1 cases.

In contrast to the findings in humans, no changes in HDC positive neurons were observed in any of several narcoleptic animal models, including the hypocretin receptor 2 mutant dog, the hypocretin knock-out mouse or the orexin/ ataxin-3 transgenic mouse [33]. The increase in histamine neurons in human narcoleptics was thus not simply a compensation for the loss of hypocretin neurons. In addition, Parkinson's patients [38, 39] showed a decreased number of hypocretin neurons, but the histamine neurons in the posterior hypothalamus were relatively stable [22, 40]. We, therefore, hypothesised that the increase in histamine neurons in human narcolepsy may be linked to autoimmune response causing new neurons to be generated (as a result of increased histamine production)or 'transmitter re-specification' [41-43] (reviewed in [44]).

4. HISTAMINE N-METHYLTRANSFERASE (HMT)

4.1. HMT Mutation Associated with Intellectual Disability and Aggressive Behaviours in Humans

HMT is the key enzyme involved in the metabolism of histamine. Two homozygous HMT mutations (*i.e.* p.Gly60Asp and p.Leu208Pro) were identified in patients suffering from non-syndromic autosomal recessive intellectual disability, also known as mental retardation autosomal recessive 51 (MRT51; OMIM: 616739), in two unrelated consanguineous families [45]. The p.Gly60Asp mutation affects HMT enzymatic activity and the p.Leu208Pro mutation results in misfolding and rapid degradation of the HMT protein [45]. A recent study reported a severely intellectually disabled Dutch male with a homozygous mutation in the HMT gene, who demonstrated the same behavioural phenotype as HMT-associated MRT51 [46]. Additionally, this case was characterized with autism, dysregulation of sleep-wake states and aggressive behaviours, including self-injury [46]. All these symptoms were found to be associated with high histamine levels because the sleep-wake cycle disturbance and aggressive behaviours were effectively treated with the

antihistaminergic compound hydroxyzine, in combination with a histamine-restricted diet [46].

4.2. HMT Knockout Mice Exhibit Sleep-wake Disorders and Aggressive Behaviours

HMT knockout animals showed elevated histamine concentrations in the brain [47]. In line with the augmented histamine concentrations, the HMT knockout mice exhibited prolonged awakening during the light (inactive) period and more sleep during the dark (active) phase [47].

Histamine neurons appear in rats on embryonic day 13; histamine immunoreactive nerve fibres are visible in embryonic day 15 [48]. Histamine facilitates *N*-methyl-*D*-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) *via* H_3R receptors during the second postnatal week, but inhibits synaptic plasticity at later developmental stages [49]. Histamine concentration was more than 6-fold higher in HMT knockout neonate mice compared to age-matched wild type mice [47]. Deficiency in the enzyme that inactivates histamine may have a negative influence on brain development, leading to impaired cognitive and behavioural phenotypes.

HMT knockout mice, with higher brain histamine levels displayed high levels of aggression in the resident-intruder and aggressive biting behaviour tests [47]. Conversely, H_1R receptor knockout mice with stable brain histamine levels were less aggressive in the resident-intruder test [50, 51]. Lower brain histamine levels were also observed in the H_3R knockout mice, where the aggression behaviour phenotypes were unfortunately not studied [52, 53] However, a novel H_3R knockout zebrafish exhibited reduced aggression in the mirror-induced aggression behaviour test [54]. Huntington's disease patients showed increased neuronal histamine production as reflected by elevated HDC-mRNA expression [55] and elevated CSF levels of histamine metabolites [56]. Upregulation of the histamine system in Huntington's patients may therefore be involved in the aggressive behaviours of this disease.

5. HISTAMINE RECEPTORS

5.1. The H_1R Antagonist, Doxepin, Alleviates Symptoms of Insomnia

The over-the-counter antihistamine, diphenhydramine, used to relieve allergies, has H_1R antagonistic activity and is able to penetrate the blood-brain barrier [57]. In addition, the antidepressant, doxepin, which affects cholinergic, dopaminergic, serotoninergic and adrenergic receptors, is also a selective H_1R antagonist [58]. Both doxepin and diphenhydramine increased non-rapid eye movement sleep in wild type mice but not in H_1R knockout mice, suggesting that they act through the H_1 receptor [59]. Consistent with this preclinical finding, a randomized, placebo-controlled trial in patients with chronic primary insomnia showed that doxepin prevented early morning awakenings as well as improved sleep in the latter part of the night [60]. Several other studies showed similar improvement in sleep maintenance and sleep duration with doxepin compared to placebo [61-65]. The U.S. food and drug administration (FDA) has approved doxepin for the clinical treatment of insomnia [66].

5.1.1. H_1R Modulation of Cognition and Mood

Recently, a comprehensive study showed that selectively knocking out H_1R in mouse basal forebrain cholinergic neurons resulted in sensorimotor gating deficit, social impairment and anhedonia-like behaviours (Cheng *et al.*, 2021). This is consistent with the finding that schizophrenic patients who suffer from negative symptoms had lower H_1R mRNA in the cholinergic neurons of the nucleus basalis of Meynert (Cheng *et al.*, 2021). This effect is cholinergic cell-specific because targeted deletions of H_1R in glutamatergic or dopaminergic neurons did not show sensorimotor gating deficits (Cheng *et al.*, 2021). Indeed, patients with varied neuropsychiatric disorders exhibit reductions of H_1R binding in a brain region-specific manner. Positron emission tomography studies showed that H_1R binding was much lower in the frontal cerebral cortex of depressed patients compared to matched controls [67, 68]. Interestingly, H_1R binding in the frontal cortex and cingulate gyrus decreased in relation to self-rated depressive scale scores [67]. Reduced H_1R binding has also been reported in the frontal and temporal brain areas of AD patients [69]. More importantly, there is a correlation between H_1R binding and the severity of cognitive deficits [69]. Although changes in H_1R binding have been reported in these patients, no changes in H_1R mRNA levels were observed in the frontal cortex of depressed (Shan *et al.*, 2013a) or AD patients in our postmortem studies (Shan *et al.*, 2012b).

5.2. H_2R has no Effect on Schizophrenia

H_2R antagonists are widely used for the treatment of gastric disorders [70]. H_2R knockout mice showed cognitive deficits in object recognition and Barnes maze tests, indicating an impairment in hippocampal LTP [71]. Although earlier studies supported the finding that the H_2R antagonist, famotidine, exhibited antipsychotic effects and reduced symptoms of schizophrenia in preliminary open-labelled clinical trials [72-75], a meta-analysis, based on 8 double-blind randomized placebo-controlled trials, concluded that H_2R-antagonists did not have any effect on schizophrenic symptoms [76]. This is in line with the fact that none of the polymorphisms in H_2R has been consistently linked to psychotic symptoms in schizophrenia [77, 78].

5.3. The H_3R Antagonist/Inverse Agonist, Pitolisant, Reduces Symptoms of Narcolepsy

By far, the most successful clinical application of the H_3R antagonist/inverse agonist, pitolisant, is in the treatment of narcolepsy. As we mentioned, narcoleptic patients lose up to 90% of their hypocretin cells, which results in their inability to stay awake [27, 28]. We speculate that the H_3R-antagonist/inverse agonist, pitolisant, used to treat excessive daytime sleepiness in narcoleptics, acts by stimulating adjacent histaminergic neurons, and thus reduces the transition to rapid eye movement sleep [79-81]. PD patients have disrupted circadian rhythmicity of HDC activity [14] as well as loss of hypocretin neurons [38, 82]. We hypothesize that H_3R-antagonist/inverse agonists may work in a similar manner to alleviate excessive daytime sleepiness in PD patients [83]. Although patients with preclinical AD, as well as animal models of schizophrenia, showed cognitive improvements with H_3R-antagonist/inverse agonists [83, 84], the clinical

results were less convincing. Furthermore, H_3R-antagonist/inverse agonists failed to reduce the cognitive deficits in patients with AD, in several randomized controlled trials [85-87]. A randomized double-blind placebo-controlled study also showed a lack of cognitive improvement in schizophrenia patients by an H_3R-antagonist [88, 89].

5.4. H_4R a Promising Therapeutic Target for PD

Loss of dopaminergic neurons in the mesencephalon leads to motor deficits in Parkinson's disease (PD) [3, 90]. Dr Panula's group previously observed increased density of histaminergic fibers in the substantia nigra, [91] and enhanced histamine levels in the basal ganglia [92] of postmortem brains of PD patients. Augmented histamine stimulated pro-inflammatory microglial activity and accelerated degeneration of dopamine neurons in the substantia nigra of animal models [93-95]. By inhibiting endogenous neuronal histamine production, dopaminergic neurons in substantia nigra of the 6-hydroxydopamine (6-OHDA)-lesioned rat were partially protected from degeneration [96]. However, to clinically inhibit endogenous neuronal histamine production would be rather difficult. An alternative approach is to determine which histamine receptor is involved in the pro-inflammatory microglial activity process.

Recently, our group showed for the first time that the H_4R is a promising therapeutic target in the treatment of PD. Using quantitative PCR (qPCR), our group observed that H_4R-mRNA levels were higher in the basal ganglia of 7 PD compared to 7 control postmortem brains [97]. Recently, using unbiased transcriptome wide RNA-sequencing, we confirmed this upregulation of H_4R-mRNA levels in the basal ganglia of another 10 PD and 10 control brains [98]. Furthermore, the H_4R antagonist, JNJ7777120, has been reported to inhibit dopaminergic neuron degeneration in a rat model of rotenone-induced PD [99]. In addition, we have shown that an H_4R antagonist inhibited pro-inflammatory microglia activation in the substantia nigra and striatum, as well as reduced Lewy body-like PD neuropathology [98, 99]. Together these results pave the way for clinical testing of the H_4R antagonist in PD.

CONCLUSION

The brain histaminergic system plays a pivotal role in the pathogenesis of several neuropsychiatric disorders, including narcolepsy, schizophrenia, depression, HD, AD and PD. By targeting the histaminergic system in the brain, novel therapeutic interventions may be developed to treat these disorders. Here, we summarized two successful clinical treatments; three preclinical findings to be followed with clinical trials; and several open issues warranting further study.

Two successful clinical treatments: 1) The H_1R antagonist, doxepin, has been approved by the FDA for the treatment of insomnia. 2) Both FDA and European medicines agency (EMA) have approved the H_3R-antagonist/inverse agonist, pitolisant, for the treatment of excessive daytime sleepiness in narcolepsy.

Three preclinical findings potentially lead to clinical treatments: 1) Loss of diurnal HDC-mRNA rhythmicity in neurodegenerative disorders, including AD, PD, preclinical PD, and HD, may contribute to the restless nights and listless days frequently seen in these patients. The H_3R-antagonists/inverse agonists are making advances in the treatment of excessive daytime sleepiness in PD. 2) The negative symptoms of schizophrenia were directly related to lower H_1R levels in the basal forebrain cholinergic neurons. 3) The H_4R antagonist could be a potential target for PD, by inhibiting inflammation and thereby protecting dopaminergic neurons from degeneration.

Open issues warranting further study: 1) Increased number of histaminergic neurons (marked by HDC immunoreactivity) in narcolepsy patients may be linked with their unique pathogenesis. 2) In addition, human HMT mutations associated with intellectual disability, dysregulation of sleep-wake states and aggressive behaviours, warrant further studies in animal models. 3) HD patients showed elevated HDC-mRNA levels and histamine metabolites, which may be involved in the aggressive behaviours of these patients. 4) Depressed patients showed a reduction of H_1R binding in the cerebral cortex, which may imply that H_1R availability is associated with mood states. 5) Preliminary results showed that the H_2R-antagonist reduced schizophrenic symptoms, but more comprehensive clinical trials failed to show any positive effects.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
CSF	=	Cerebrospinal Fluid
$H_{1\text{-}4}$R	=	Histamine 1-4 receptors
H_1R antagonist	=	Doxepin
H_2R antagonist	=	Famotidine
H_3R antagonist	=	Inverse Agonist Pitolisant
H_4R antagonist	=	JNJ7777120
HDC	=	l-histidine decarboxylase
HMT	=	Histamine N-methyltransferase
mRNA	=	Messenger RNA
PD	=	Parkinson's Disease
t-MeHA	=	Tele-methylhistamine
TMN	=	Tuberomamillary Nucleus

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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