Review

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The human histaminergic system in neuropsychiatric disorders

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Histaminergic neurons are exclusively located in the hypothalamic tuberomamillary nucleus, from where they project to many brain areas. The histaminergic system is involved in basic physiological functions, such as the sleep–wake cycle, energy and endocrine homeostasis, sensory and motor functions, cognition, and attention, which are all severely affected in neuropsychiatric disorders. Here, we present recent postmortem findings on the alterations in this system in neuropsychiatric disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), depression, and narcolepsy. In addition, we highlight the need to validate animal models for these diseases and also for Tourette's syndrome (TS) in relation to alterations in the histaminergic system. Moreover, we discuss the potential for, and concerns over, the use of novel histamine 3 receptor (H_3R) antagonists/inverse agonists as treatment for such disorders.

Human neuronal histaminergic system

The neuronal histaminergic system is involved in several functions, such as the sleep–wake cycle, energy and endocrine homeostasis, sensory and motor functions, cognition, and attention, all of which tend to be severely affected in neuropsychiatric disorders, such as PD, AD, HD, depression, and narcolepsy. This system has been the subject of several reviews [1–3], such as one by Haas *et al.*, which mostly summarized animal experimental findings before 2008 [1] and two by Panula *et al.*, one that focused on the role of brain histamine in several disorders, including sleep, cognitive, and motor disorders, and addiction, largely based upon data from animal studies [2], the other on the developmental role of brain histamine [3]. However, none of these reviews mainly focused on postmortem findings. Thus, here we first discuss postmortem data concerning the human brain histaminergic system in health and disease. Second, we pay special attention to the validation of animal models of histaminergic system involvement in neuropsychiatric disorders. Recently, a mutation in the gene encoding L-histidine decarboxylase (HDC), the rate-limiting enzyme for the synthesis of histamine [4], has been found to be closely correlated with familial TS. However, the phenotype of the HDC-knockout mouse, which has a functional mutation of the same gene, needs to be validated to be used as a model for TS [4,5] (see section below on TS). In addition, two postmortem studies have recently demonstrated a robust increase in histaminergic neurons in the tuberomamillary nucleus (TMN) of narcoleptic brains [6,7], but animal models for narcolepsy showed no change [6] or only a slight increase in the number of these neurons [7]. Third, because H_3R antagonists/inverse agonists are currently advancing into clinical trials as a potential treatment for AD, PD, and narcolepsy [8,9], we present a timely discussion of their potential as well as any concerns associated with these compounds.

Histamine synthesis

Anatomy and properties of human TMN

Histaminergic neurons are exclusive to the hypothalamic TMN, which is located in the posterior hypothalamus (Figure 1A). The human TMN is characterized by its typical lipofuscin-laden neurons, with intense Nissl staining of the endoplasmic reticulum localized in the periphery of the cytoplasm, interspersed with the typical irregularities in the cell membrane (Figure 1B,C). Studies using either Nissl staining [10] or histamine immunoreactivity [11] to examine tissue from neurological and psychiatric disease-free subjects suggest that there are between 32 000 and 42 000 neurons on one side of the hypothalamus. TMN neurons surround the lateral tuberal nucleus, the fornix in its final descending course, and the mamillary body. Histaminergic fibers have been found in many brain

Glossary

Radioactive *in situ* hybridization (ISH): enables specific nucleic acid sequences to be detected in morphologically well-preserved tissue sections. This technique is widely used to detect the expression of specific genes at the mRNA level. When relative quantitative comparison between experimental groups is needed, radioactive ISH still holds an advantage of signal quantification on paraffin-embedded tissue sections, which have practical advantages for anatomically complex structures, such as the human hypothalamus, with regard to anatomical orientation and the study of archival material.

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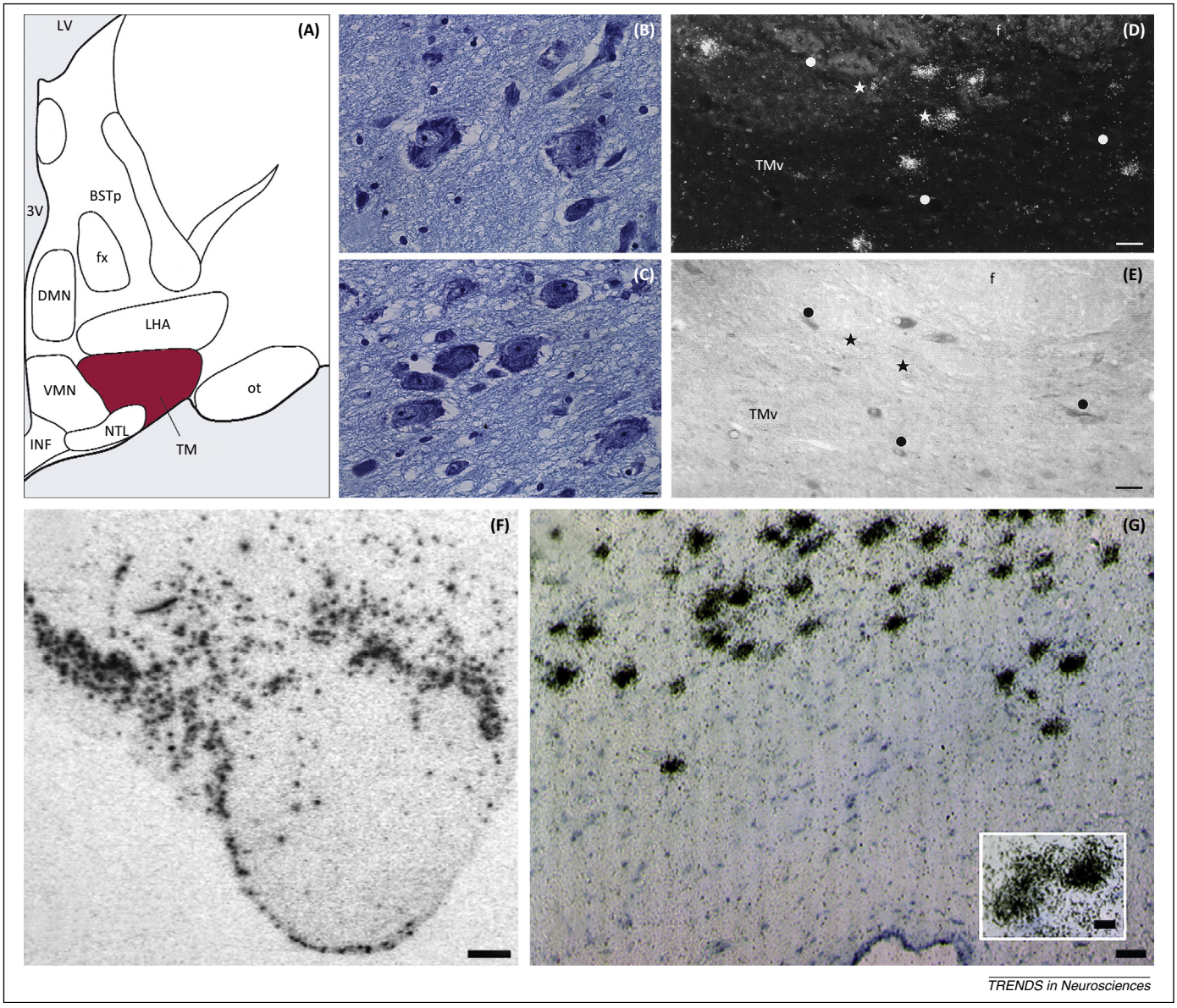


Figure 1. Location of human tuberomamillary nucleus (TMN), typical TMN neurons, and the colocalization of histidine decarboxylase (HDC) with GABA. **(A)** Scheme of coronal section of the human hypothalamus at the level of the TMN that is highlighted. **(B,C)** Examples of Nissl staining of TMN neurons showing intensely stained endoplasmic reticulum interspersed with the typical irregularities in the cell membrane. **(D,E)** Co-expression of HDC mRNA (D) and glutamic acid decarboxylase (GAD)-67-like immunoreactivity (E) in two consecutive sections of the ventral TMN. **(F,G)** Specific HDC mRNA radioactive *in situ* hybridization signal observed in the TMN both on film autoradiograms (F) and after emulsion autoradiography with thionin-counterstaining (G). Scale bars = 5 μm (B,C), 50 μm (D,E), 1 mm (F), 50 μm (G). and 12.5 μm in insertions. Abbreviations: BSTp, bed nucleus of stria terminalis posterior; DMN, dorsomedial hypothalamic nucleus; fx or f, fornix; INF, infundibular nucleus; LHA, lateral hypothalamus; LV, lateral ventricle; NTL, lateral tuberal nucleus; OT, optic tract; TM, tuberomamillary nucleus; TMv, ventral TM; VMN, ventromedial hypothalamic nucleus; 3 V, third ventricle. Adapted, with permission, A from [94]; D and E from [17]; and F and G from [25].

areas, including the prefrontal cortex (PFC), thalamus, and substantia nigra (SN) [12–14].

Histamine in the TMN is synthesized from the amino acid histidine by HDC [15] and HDC knockout or pharmacological manipulation of HDC significantly decrease histamine production in rodents [16]. In the human TMN, a large proportion of histaminergic neurons colocalize GABA, as indicated by the presence of the GABA synthesizing enzyme glutamic acid decarboxylase [17] (Figure 1D,E). In addition, acetylcholinesterase [18], monoamine oxidase [19], cocaine and amphetamine-regulated transcript [20], and galanin [21] have been observed in the human TMN.

Histamine synthesis in the TMN: diurnal fluctuation

The activity of histamine neurons increases in the active period in several species. For example, in the TMN of nocturnal rodents, an increase in neuronal activity was observed during the dark period [22]. In addition, compared with the sleep stage, microdialysis and quantitative radioenzymatic assays revealed a considerably higher histamine concentration in the cat preoptic–anterior hypothalamic area during waking [23], while a daytime increase in the main histamine metabolite tele-methylhistamine (t-MeHA) was found in the cerebrospinal fluid (CSF) of diurnal rhesus monkeys [24]. Following optimization of a radioactive *in situ* hybridization (see Glossary)

protocol [25], we observed, in formalin-fixed, paraffin-embedded postmortem human brain tissue, that the total expression of HDC mRNA in the TMN (Figure 1F,G) exhibits higher levels during the day and lower levels during the night in subjects without a neurological or a psychiatric disease [26] (Figure 2A). In a group of patients with various neurodegenerative disorders, this diurnal rhythm was absent (Figure 2A), which may contribute to the sleep disorder in these diseases. Interestingly, a circadian rhythm is present in CSF-histamine levels in the squirrel monkey, with a peak value around 17:49 h [27], which fits well with the highest value of HDC mRNA expression observed in the human TMN around 18:09 h (Figure 2B). In addition, the finding that HDC mRNA expression reaches its lowest level around 01:09 h is in agreement with a previous finding that the TMN had its lowest activity during sleep [22]. These data support the idea that TMN neurons promote wakefulness and have an important role in the regulation of day–night patterns [22]. Moreover, they support the idea that postmortem data may reflect day–night fluctuations during life, which was also found earlier for the biological clock, the suprachiasmatic nucleus [28], and recently for gene expression throughout the brain [29].

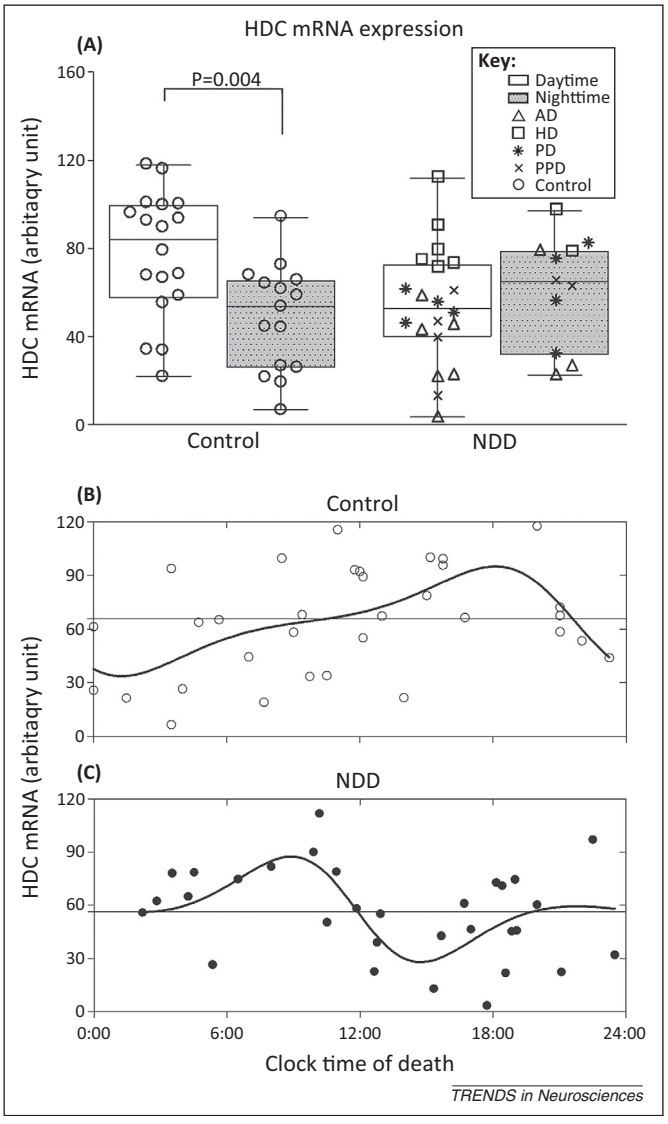


Figure 2. Diurnal rhythm of histidine decarboxylase (HDC) mRNA expression. **(A)** Box plots show the median, 25th–75th percentiles and the total range of radioactivity of HDC mRNA expression in arbitrary units. The total amount of HDC mRNA expression is given for control subjects between daytime (08:01–20:00 h; $n = 18$) and nighttime (20:01–08:00 h; $n = 15$) on the left side, and for neurodegenerative diseases group (NDD, daytime $n = 20$, nighttime $n = 11$) on the right side. Note that there is a significant difference ($P = 0.004$) between daytime and nighttime in control subjects, but not in NDD ($P = 0.410$). **(B,C)** Raw data of HDC mRNA expression plotted along the clock time of death. The nonlinear periodic functions describe the circadian cycles. The model in controls (unfilled dots) reach an estimated maximum at the end of the afternoon (T_{max} = 18:09 h) and a minimum shortly after midnight (T_{min} = 1:09 h) (B). The model in the NDD group (filled dots) reaches an estimated maximum in the morning (T_{max} = 8:56 h) and a minimum in the afternoon (T_{min} = 14:43 h). The horizontal lines indicate the 24-h mean of HDC mRNA expression in controls and NDD group respectively. Modified, with permission, from [26].

However, alterations in histamine-related gene transcript levels, such as HDC mRNA levels, that are measured post mortem are only an indication of the changes in local histamine levels. The relation between the levels of these transcripts and of histamine may be complex: histamine levels fluctuate over the course of the day [24,26,27], different steps are involved from transcription to translation, and to enzymatic breakdown, which will eventually be reflected in the local histamine levels. Given that the short half-life of brain histamine hampers its measurement in the postmortem human brain, a combination of these transcript levels and CSF levels of histamine and histamine metabolites may help to estimate the activity, in the postmortem brain, of the histaminergic system.

Histamine receptors and metabolism

Given that the signaling and downstream pathways of the G protein-coupled histamine receptors and of histamine metabolism have been extensively reviewed elsewhere [1,2], we briefly review their characteristics in human brain in Box 1.

The histaminergic system in neuropsychiatric disorders

Parkinson's disease

PD is characterized by distinctive motor symptoms, mainly caused by loss of dopaminergic neurons in SN, including: tremor at rest, bradykinesia, rigidity, flexed posture, loss of postural reflexes, and freezing of gait [30]. In one of the PD animal models [i.e., the 6-hydroxydopamine (6-OHDA)-lesioned rat], an increase in endogenous histamine appeared to enhance apomorphine-induced turning behavior and to increase the loss of tyrosine hydroxylase (TH) in the SN [31]. In addition, in this model, injection of α-fluoromethylhistidine, an irreversible inhibitor of HDC, at an early stage of the disease strongly reduced rotation behavior and prevented the loss of TH-expressing cells [32]. Given the data obtained in this PD animal model, postmortem observations showing an increased histamine activity in PD [12,33] suggest a possible negative influence of the histaminergic system on PD progression.

However, a postmortem study of both patients with preclinical and clinical PD showed no significant changes in TMN HDC mRNA expression [34]. Interestingly, the unaltered expression of HDC was combined with a strong accumulation of Lewy bodies (LBs) and Lewy neurites (LNs), which are characteristic neuropathological PD markers that occur early in the disease process in the TMN [34,35] (Table 1). Thus, these data suggest that there is no increase in endogenous histamine production during the

course of PD, which is in line with findings of intact numbers of histaminergic neurons [36], the unchanged enzyme activity of HDC [37], and the unaltered CSF t-MeHA levels in PD [38]. Some studies reported an increased density of histaminergic fibers in the SN [39,12] and increased local histamine levels in the SN of patients with PD [33]. This led to an investigation of the striatum of such PD, which found an upregulation of histamine *N*-methyltransferase (HMT) mRNA in the SN and putamen [40]. In addition, we observed significantly decreased H_3R mRNA in the SN in PD [40] (Table 1). H_3R immunoreactivity appeared to be exclusively localized in the large neuromelanin-containing neurons in the SN of both control patients and patients with PD, which may explain the decreased H_3R mRNA expression in the SN. Taking these data together, one may propose that, although histamine production (estimated as HDC mRNA) in the TMN does not change significantly in PD, there might be an increased local release of histamine in the SN and putamen. This increased local histamine is not only apparent from the higher density of histaminergic fibers [39,12] and the higher local histamine levels in the SN of patients with PD [33], but also from the increased HMT mRNA, which may be due to the higher histamine levels [40]. Therefore, findings in the human SN are largely in agreement with findings in the PD animal model mentioned above; that is, that the increased histamine levels in the SN may contribute to an accelerated degeneration of dopaminergic neurons [32,41]. Thus, concerning the ongoing phase III clinical trials of H_3R-antagonists/inverse agonists for the excessive daytime sleepiness in PD [8], one must keep in mind that such compounds may induce an increased local release of histamine and, thus, cause accelerated degeneration of dopaminergic neurons.

Alzheimer's disease

AD is the most common form of dementia, initially presenting with short-term memory impairment. The reports on the alterations in the histaminergic system in AD vary (Table 1). Some studies reported a hyperactive histaminergic system during aging [42] and in AD [43,44] with increased CSF histamine levels and increased histamine metabolites in the frontal cortex, basal ganglia, and hippocampus [43,44]; others reported diminished histamine levels in AD (e.g., in the hippocampus, frontal, and temporal cortex [45,46]). In addition, a loss of large histaminergic neurons in the rostral TMN in AD was observed [47]. These discrepancies might be, at least partly, explained by putative confounding factors in the postmortem studies, such as postmortem delay (PMD), gender ratio, and age, together with the diurnal fluctuation of the histaminergic system in the brain [26].

A significant (57%) loss of TMN neurons in Braak VI (i.e., the final stage of AD) [35] in a cohort of postmortem AD brains has been observed, whereas no significant changes were found in HDC mRNA expression in the TMN compared with controls [10]. This implies that, in terms of histamine production, the significant loss of TMN neurons in AD is largely compensated for by the remaining TMN neurons. This is in agreement with the finding in a large cohort study that patients with AD had a slightly but not significantly (22%) lower level of lumbar CSF t-MeHA compared with controls [48]. In the PFC, an important brain area for cognition, we observed a significant increase in H_3R and HMT mRNA expression, although only in female patients in the late stages of AD (Braak stages V and VI). In addition, significant positive correlations were found in female, but not in male, patients with AD between H_3R mRNA levels and Braak stages, and between HMT

Box 1. Histamine receptors and metabolism

Histamine receptor 1

The function of H_1R is reflected by the adverse effects of classic antihistamines (i.e., sleepiness and cognitive deficits) [95]. H_1R-knockout mice showed disturbed circadian rhythms of food intake [96] and locomotor activity [97]. In addition, long-term potentiation was decreased in the hippocampal cornu ammonis of H_1R- and H_2R-double knockouts [98], which may underlie poorer learning and memory. In the postmortem human neocortex, the highest H_1R binding was observed in layers V and VI, while the claustrum, hippocampal formation, thalamus, and globus pallidus also showed high levels of H_1R-binding [99].

Histamine receptor 2

H_2R-knockout mice showed impaired cognition and nociception [1]. H_2R expression is decreased in HDC-knockout mouse brain [100], which is an indication of its close relation with the amount of neuronal histamine. Indeed, dense histaminergic innervation and high H_2R binding are present in human cerebral cortex layers I and II [13].

Histamine receptor 3

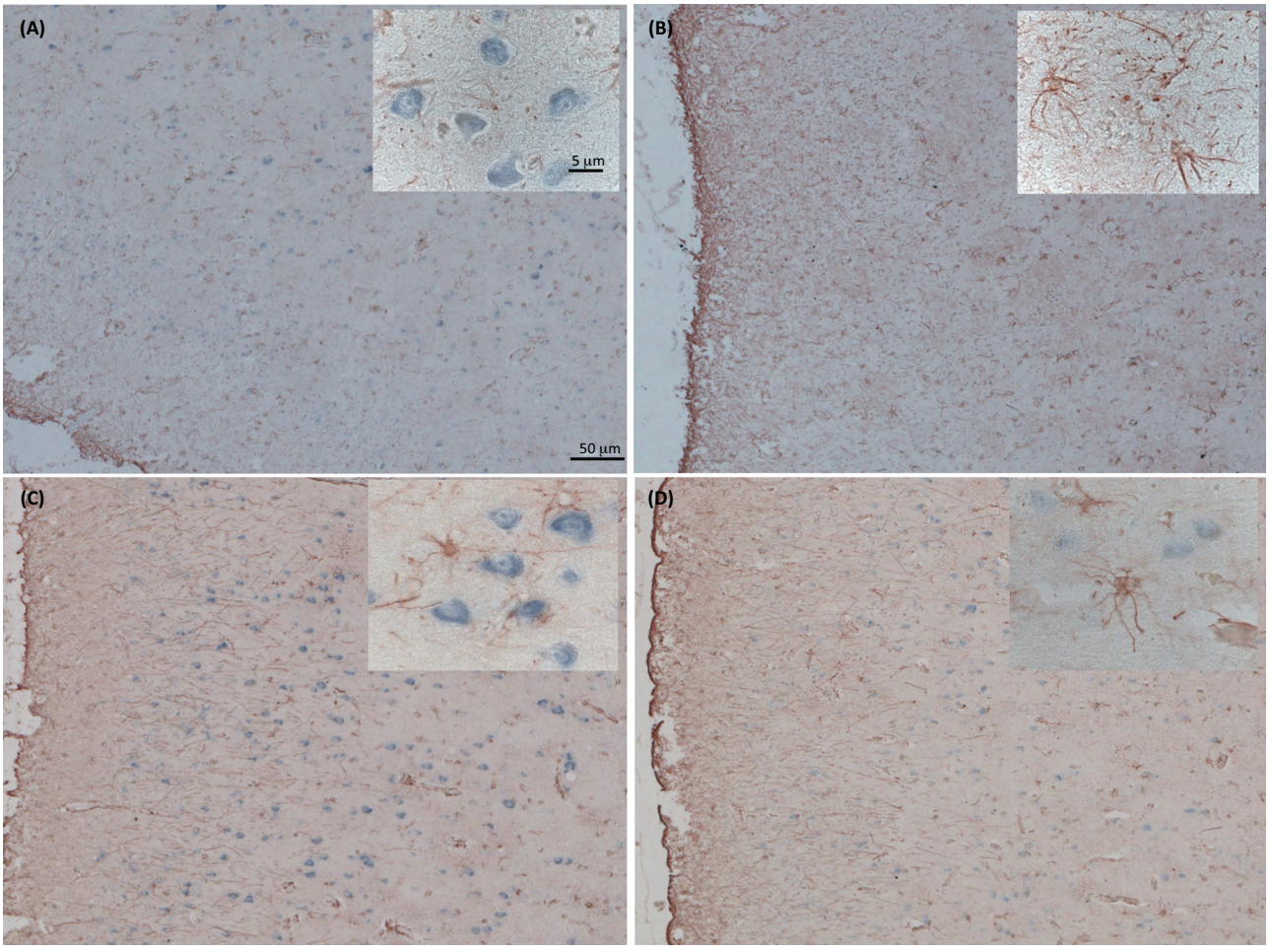
In human postmortem brain, higher H_3R binding was observed in cerebral cortex layers III and IV and in the thalamus [101]. Both H_3R mRNA and H_3R protein expression were higher in the putamen than in SN or in caudate [40], which is in agreement with previous studies [39,102,103]. H_3R is distributed not only as an autoreceptor localized on somata, dendrites, and axons of the TMN neurons, but also as a postsynaptic receptor localized on nonhistaminergic neurons in several brain areas, regulating the release of neurotransmitters such as GABA, glutamic acid, acetylcholine, and noradrenaline [104–106] (reviewed in [2]). In rodents, H_3R antagonists/inverse agonists increased the release of neuronal histamine, acetylcholine, and dopamine in different brain areas [104–106], improving cognitive performance in various cognition paradigms [104]. Therefore, H_3R antagonists/inverse agonists have been introduced into clinical trials to treat symptoms such as sleep–wake disorders in PD and narcolepsy, and cognitive disorders in AD, schizophrenia, and attention-deficit hyperactivity disorder [9]. However, no significant improvement of cognition was observed after administration of H_3R antagonists/inverse agonists in recent clinical trials with patients with AD or schizophrenia [54,107].

Histamine receptor 4

Information about H_4R, functionally expressed in the human brain [108,109] is limited and controversial [110]. A relatively high expression of H_4R has been reported in human cortex layers VI and V [109]. Increased H_4R mRNA expression was also found in the striatum in PD [40], warranting further studies on H_4R.

Histamine *N*-methyltransferase

Histamine is rendered inactive in the brain by HMT. Given that inhibition of astrocyte function may enhance the extracellular concentration of histamine, the astrocyte was proposed to be the main inactivation site of histamine [111,112]. However, in postmortem human PFC, despite the strong positive correlation between levels of HMT mRNA and mRNA levels of the astrocyte marker glial fibrillary acidic protein, both in controls and in patients with AD, HMT mRNA was localized only in neurons and not in astrocytes (Figure I) [10].



TRENDS in Neurosciences

Figure I. Glial fibrillary acidic protein (GFAP) immunocytochemistry and histamine methyltransferase (HMT) mRNA *in situ* hybridization (ISH) in the human prefrontal cortex (PFC). **(A)** Specific HMT mRNA ISH signal (blue) was observed in neurons only after hybridization with HMT antisense probe in the PFC of a patient with Braak stage 6 Alzheimer's disease with GFAP (red) double staining. Inset shows detail of the HMT mRNA neuronal staining and astroglial GFAP staining. **(B)** Absence of blue staining after hybridization with scrambled probe in adjacent section from the same subjects. Inset shows detail about the absence of HMT-mRNA neuronal staining and positive astroglial staining. **(C,D)** Representative double staining in a control subject and a Braak stage 3 subject. Insets show detailed HMT mRNA neuronal staining and GFAP astroglial cell staining, respectively. Scale bar for A–D = 50 μm; scale bar for insets = 5 μm. Modified, with permission, from [10].

mRNA levels and Braak stages [10], indicating a sex difference in the etiology of AD in relation to the histamine system.

Several AD mouse models have been developed that exhibit one or more of the neuropathological hallmarks of AD (i.e., amyloid-β protein deposition or tau hyperphosphorylation) [49]. So far, there is limited information concerning histaminergic system changes in these models and there is no AD animal model showing similar alterations to those found in the histaminergic system in patients with AD. For example, the transgenic mouse model with overexpression of APP695 Swedish mutation and presenilin-1 M146V mutation showed unchanged H_3R binding in the cortex [50], which is similar to the finding of insignificant changes in H_3R-binding density in the postmortem PFC of patients with AD [51]. The possible presence of sex differences as observed in the PFC of patients with AD (see above) [10] has not yet been investigated in this animal model.

Interestingly, the H_3R antagonist ciproxifan improved the cognitive performance of APP_{Tg2576} mice [52] and infusion of the H_3R antagonist ABT-239 was found to reverse tau hyperphosphorylation in spinal cord and hippocampus of TAPP (tau×APP) AD transgenic mice [53]. The animal data and human postmortem data seem to provide a rationale for the use of H_3R antagonists, in particular in female patients with AD, to improve cognitive processes in the PFC, because H_3R regulates the release of several neurotransmitters (Box 1) and AD is reported to be associated with decreased release of histamine, acetylcholine, noradrenalin, and dopamine [8]. However, the unchanged HDC mRNA expression in the TMN [10] seems to indicate compensatory activation of the remaining TMN neurons. Thus, administration of an H_3R antagonist may cause overactivation of these neurons, which could accelerate their degeneration. By contrast, the expected positive effects of H_3R antagonists on AD might be modest in view of the small increase in H_3R mRNA in female patients with AD [10] and the insignificant changes of H_3R-binding density in the PFC reported by another postmortem study [51]. Indeed, in several recent randomized controlled trials, H_3R antagonists/inverse agonists appeared to be ineffective

Table 1. Overview of alterations of brain histaminergic system in neuropsychiatric disorders[a]

Disorder	Postmortem			*In vivo*	
	Histamine production		Histamine projection brain areas	Spinal CSF	
	TMN neurons	HDC mRNA		Histamine	t-MeHA
PD	– (↑ LB, LN) [35,36]	– [34]	SN (mRNA HMT ↑; H_3R ↓ [40], HA level ↑ [33]; H_3R binding ↑ [39])		– [38]
			PU mRNA (HMT ↑; H_3R ↓; H_4R ↑) [40], HA level ↑ [33]		
			CN mRNA (H_4R ↑) [40], HA level – [33]		
AD	↓ (–57%) (↑ NFT) [10]	–/↓ (–20%) [10]	SPFC mRNA (HMT and H_3R ↑) [10], HA level in brain ↑ [43]/↓ [46]		–/↓ (–22%) [48]
HD	– (mutant Huntingtin) [61]	↑ (+63%) [61]	IFG mRNA (H_1R ↑; H_3R ↑; HMT ↑); CN mRNA (H_2R ↓; H_3R ↓) [61], H_2R and H_3R binding ↓ [59]; H_1R binding ↑ [60]		↑ [62]
Depression	– [76]	– [76]	– DLPFC and ACC mRNA (HMT ↑)[76]; H_1R binding by PET scanning ↓ [75]		N/A
Narcolepsy	64 or 94% ↑ [6,7]	N/A	N/A	– [87]/↓ [86,113]	– [87]

[a]Abbreviations: ↑, increase; –, stable; ↓, decrease; CN, caudate nucleus; DLPFC, dorsal lateral PFC; IFG, inferior frontal gyrus; LB, Lewy bodies; LN, Lewy neurites; PU, putamen; NFT, neurofibrillary tangles; SPFC, superior PFC.

improving cognition in patients with mild to moderate AD [54–56].

Huntington's disease

HD is an autosomal dominant hereditary neurological disorder caused by expanded CAG repeats in the huntingtin gene. Patients with HD show random and uncontrollable movements, called chorea. The histaminergic system is presumed to be involved in HD because the TMN contains the highest density of nuclear and cytoplasmic inclusions of mutant huntingtin, the neuropathological hallmark of HD (Figure 3) [57]. Postmortem studies have shown that both H_2R [58] and H_3R [59] were decreased in many brain regions, especially in the striatum, while H_1R was increased in cortical areas of patients with HD [60]. Increased HDC mRNA levels were observed in the TMN, together with an increase in HMT, H_1R, and H_3R mRNA levels in the inferior frontal gyrus (IFG) of patients with HD (Table 1) [61]. Given that the levels of histamine metabolites in CSF are also increased in patients with HD [62], an enhanced activity of the neuronal histaminergic system seems to be present in this condition.

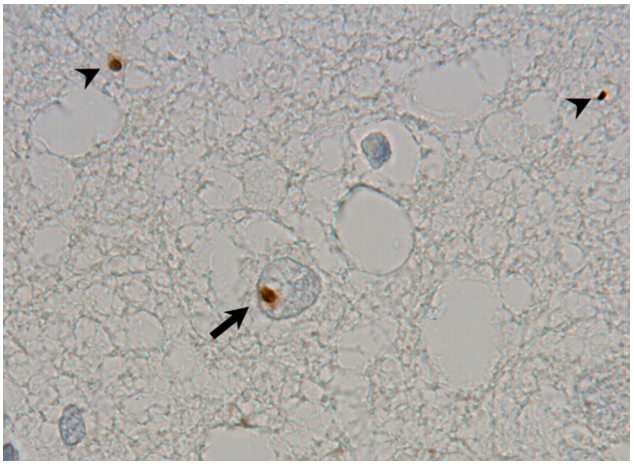


Figure 3. Example of neuronal intranuclear (arrow) and cytoplasmic (arrowheads) inclusions of mutant huntingtin in the tuberomamillary nucleus (TMN)of a patient with Huntington's disease. Reproduced, with permission, from [57].

In the transgenic HD mouse model R6/2, a reduction in hypocretin/orexinergic (Hcrt) neurons was observed [63], which are adjacent to, and reciprocally connected with, the TMN [15,64]. Both systems are involved in the regulation of the sleep–wake cycle [1,2]. This is in agreement with the reduction of Hcrt neurons observed in patients with HD [57]. The input of Hcrt fibers to the TMN area was also significantly decreased in the R6/2 animal model [65]. It is at present unclear whether the histaminergic system is altered in this HD mouse model. The postmortem finding of an activation of the histaminergic system in HD still needs to be validated in HD animal models.

Depression

Stressful life events are one of the main precipitants of depression. The hypothalamic paraventricular nucleus (PVN) is a key regulating system for the stress response and is known to be overactivated in depression [66,67]. Interestingly, following intracerebroventricular infusion of histamine in rats, there was increased mRNA expression of the stress-related neuropeptides corticotropin-releasing hormone (CRH), arginine vasopressin, and oxytocin in the PVN and oxytocin in the supraoptic nucleus induced via H_1R and H_2R [68].

Brain histamine may have a role in acute and chronic stress in animals (reviewed in [69]). Early experimental evidence has shown that hypothalamic histamine significantly increases in rats exposed to acute stress [70,71]. In addition, it was found that acute stress increased the histamine level in the rat cerebral cortex [72], diencephalon, and nucleus accumbens (NAc) [73]. Moreover, HMT activity increased in the rat NAc and striatum under both acute and chronic restraint stress [69]. Consistent with this, histamine and t-MeHA were significantly increased in the mouse cerebral cortex following a forced swimming test [74], which is an acute stressor inducing depression-like behavior.

In human patients, PET scanning showed decreased H_1R binding in the PFC and cingulate gyrus, which

correlated with the severity of the depressive symptoms [75]. However, no differences were observed in HDC mRNA expression in the TMN and there was no correlation between the levels of HDC mRNA in the TMN and the number of CRH-expressing neurons in the PVN in depressive patients (Table 1) [76]. The postmortem data of the unaltered HDC mRNA levels in depression show a discrepancy with the animal experimental models and do not support the idea that changes in the histaminergic system may have a major role in the activation of the hypothalamic–pituitary–adrenal (HPA) axis in depression.

Narcolepsy

Narcolepsy is a chronic sleep disorder that is characterized by excessive daytime sleepiness, cataplexy, depression, and other rapid eye movement (REM) sleep abnormalities, including hypnagogic hallucinations, sleep paralysis, and disturbed nighttime sleep.

Narcolepsy is a good example of how postmortem findings could increase our knowledge and direct the development of animal models. Before it had been reported that Hcrt neurons disappeared from the brain of patients with narcolepsy and cataplexy, a dog model, later linked to the mutant Hcrt receptor 2 gene, was accepted as narcoleptic animal model, because it exhibited strong cataplexy and sleep impairment similar to the symptoms of patients with narcolepsy and showed increased firing of histaminergic cells during cataplexy [77]. In 2000, postmortem human brain studies showed that 90% of the Hcrt neurons were lost in narcolepsy with cataplexy [78,79], explaining their undetectable levels of CSF Hcrt. Subsequently, several lines of rodent narcolepsy models were developed based upon the postmortem findings [80–82], such as Hcrt-knockout mice with a genetic mutation of the *Hcrt* gene resulting in the loss of Hcrt peptide expression prenatally [80]; the Ataxin-3 models with transgenic expression of a toxic protein in Hcrt neurons that causes selective degeneration of Hcrt neurons immediately after birth [81], and the Hcrt-tTA; TetO DTA mouse model with conditional ablation of Hcrt neurons by diphtheria toxin-A under the control of a tetracycline operator, the loss or prevention of loss of Hcrt neurons in this mouse can be induced at any age when doxycycline in their diet is removed or restored, respectively [82]. The Hcrt-tTA; TetO DTA mouse model is thought to more closely resemble human narcolepsy compared with the other models because of the post-pubertal onset of narcolepsy in humans.

The Hcrt system helps to maintain wakefulness, largely via TMN cells. Hcrt terminals around TMN neurons contain glutamatergic vesicles [83], and both Hcrt and glutamate excite histaminergic neurons [64,84]. Microdialysis studies showed that, in wild type mice, intraventricular administration of Hcrt causes increased histamine release from the TMN, together with much reduced REM and non-REM sleep [85]. In patients with narcolepsy, both lower CSF histamine [86] and unchanged CSF histamine and CSF t-MeHA levels [87] were reported (Table 1). This discrepancy may be caused by confounds such as age, gender ratio of the samples, and/or the time of the day when the samples were collected, as previously discussed. Recently, a strikingly increased number of HDC-expressing neurons was reported in narcoleptic postmortem brain [6,7]. However, such a robust increase in HDC-positive neurons was not present in narcoleptic animal models. The mechanism behind this observation calls for further study.

Some positive effects of H_3R- inverse agonists/antagonist have been reported for the narcoleptic rodent model and for patients with narcolepsy [88–90]. Pitolisant (BF2.649/tiprolisant/Wakix), one of the H_3R inverse agonists, was reported to enhance histamine neuronal activity, promote wakefulness, and decrease abnormal onset of REM sleep from the wakefulness in Hcrt-knockout mice [89]. In patients with narcolepsy, there were two small trials that exhibited the effect of pitolisant on the recovery from excessive daytime sleepiness [88,89]. In a larger double-blind randomized trial (HARMONY I study group), pitolisant was reported to ameliorate excessive daytime sleepiness with comparable effectiveness to that of modafinil, an approved medicine for narcolepsy [90]. Pitolisant is currently under study in various ongoing or completed clinical trials according to the National Institute of Health Clinical Trials Database (clinicaltrials.gov), which may provide more insight into the role of histamine in the excessive sleepiness and cataplexy attacks in narcolepsy.

Tourette's syndrome

TS is characterized by motor and vocal tics as well as by sensory and cognitive symptoms. The onset of tics is usually in childhood. So far, there has been no study on the histaminergic system in the postmortem brain or CSF of patients with TS. In a rare two-generation pedigree, a mutation (W317X) in one of the HDC gene alleles was associated with the occurrence of TS [4]. The phenotype of HDC-knockout mice [5] shares some symptoms with patients with TS who have the HDC W317X mutation [4]. In the HDC-knockout mice, HDC intron 5 to exon 9 is replaced by an external gene, which results in decline of histamine synthesis in several organs. The brain histamine levels of homozygote HDC-knockout mice on a low-histamine diet were 30% of those of wild type mice [91] and even negligible in a more recent study [5]. Interestingly, the heterozygote HDC-knockout mice that have intermediate brain histamine levels [5,91] exhibited stereotypies [5] and, thus, may better recapitulate the status of human carriers of the HDC W317X mutation, who still carry one wild type HDC allele. Several similarities and discrepancies between the HDC-knockout animal model and human TS with a HDC W317X mutation were discussed in detail in a recent review [92]. The most significant difference was that the spontaneous tics, characteristic of patients with TS, are absent in HDC-knockout homozygote or heterozygote mice. Tic-like symptoms (e.g., sniffing or orofacial movements) were only exhibited following intraperitoneal injection of amphetamine [5]. In addition, the translation from sniffing or orofacial movements in rodents into tic-like behavior in humans requires additional validation, because the behavior of the animal is subtle and the judgment is subjective: as in murine cataplexy behavior observation, the immobility should be accompanied by simultaneous recording of typical

Box 2. Outstanding questions

Are the observed histaminergic changes a cause, consequence, modifying factor, compensation, or an epiphenomenon of the disease process?
In view of what is currently known, this is a difficult question to answer. One way to find out, for example in a PD study, would be to explore the histaminergic changes in the SN of patients with preclinical PD, because experimental evidence and postmortem observations have shown that histamine may be involved in the acceleration of neurodegeneration in the SN in PD.

Does the significantly increased number of HDC-positive neurons in the posterior hypothalamic area in narcoleptic brains concern newly generated neurons or functional upregulation of the existing neurons?
To answer this question, experimental animal models are needed.

How does brain histaminergic system change in patients with TS?
The phenotype of heterozygote HDC-knockout mice shows similarities to the symptoms shown by patients with TS and with HDC W317X mutation. However, because such patients still carry one wild type HDC allele, which might compensate to a different degree for HDC enzyme activity and, thus, for brain histamine production, information on histamine and t-MeHA levels in CSF and in postmortem brain regions of such patients is crucial to determine the possible association between TS etiology and impaired histamine production.

How can we predict and/or evaluate the effect of H_3R antagonists/inverse agonists on neuropsychiatric disorders?
Recent clinical trials indicate that H_3R antagonists/inverse agonists do not improve cognitive functions in AD or schizophrenia, but do have an effect on excessive daytime sleepiness in PD and on narcolepsy. Experimental animal models with good consistency with postmortem histaminergic findings are required to better understand the mechanisms involved and to facilitate preclinical drug tests.

Can animal models for neuropsychiatric disorders replace postmortem human brain studies?
We do not think so. Current genetic tools enable the manipulation of specific genes or proteins in animal models, but postmortem findings remain invaluable for the development and validation of animal models, such as for narcolepsy.

signatures of electroencephalography and electromyography [93].

Concluding remarks

The human histaminergic system shows diurnal fluctuations in the TMN, which is its production site. In addition, there are changes in expression levels of HDC, $H_{1-4}R$, and HMT in various neuropsychiatric disorders that might be related to symptoms of these diseases. The animal models used for these disorders do not, or only partly, reflect the histaminergic changes in the human brain.

In the human postmortem PD brain, no indication was found for an activation of endogenous histamine production, but postmortem human brain data show there might be increased local (e.g., SN) histamine release. The animal PD model indicated that increased local histamine may accelerate degeneration of dopamine neurons in the SN (Box 2). In AD, the remaining TMN neurons showed strong compensation for histamine production, which results in insignificant changes in HDC mRNA expression in the TMN of patients with late-stage AD. In addition, higher levels of H_3R and HMT mRNA expression were found in the PFC in AD, but only in women. Currently, no AD animal data are available that show the same TMN or PFC changes as observed in humans. Patients with HD have an increased activity of the histaminergic system, which still needs to be confirmed in HD mice models. HDC expression was not altered in depression. The histaminergic changes in acute or chronic stress-induced animal models do not seem to agree with findings in depressive patients. In narcolepsy, a strong increase in the number of HDC-positive neurons has been reported in the TMN, although this is not seen in narcolepsy animal models (Box 2). The recent finding of HDC-knockout mice with symptoms similar to those of patients with TS and with the HDC W317X mutation needs to be validated, not only for behavioral changes, but also for changes in the human postmortem histaminergic system in TS (Box 2). H_3R antagonists may serve as a valuable adjunct treatment for certain symptoms in the disorders discussed. However, such compounds should be administered with the utmost caution, because of their potential adverse effects, including induction of degeneration of dopaminergic neurons in the SN in PD and overactivation of the remaining TMN neurons in AD. The augmentation of histamine observed in HD may provide a rationale for the use of H_3R agonists (Box 2).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tins.2014.12.008.

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