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Histamine and Histamine Receptors in Health and Disease

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Changes in Histidine Decarboxylase, Histamine *N*-Methyltransferase and Histamine Receptors in Neuropsychiatric Disorders

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Abstract

Compared to other monoamine neurotransmitters, information on the association between the histaminergic system and neuropsychiatric disorders is scarce, resulting in a lack of histamine-related treatment for these disorders. The current chapter tries to combine information obtained from genetic studies, neuroimaging, post-mortem human brain studies and cerebrospinal fluid measurements with data from recent clinical trials on histamine receptor agonists and antagonists, with a view to determining the possible role of the histaminergic system in neuropsychiatric disorders and to pave the way for novel histamine-related therapeutic strategies.

Keywords

Histamine • Histidine decarboxylase • Histamine receptors • Histamine *N*-methyltransferase • Neurodegenerative diseases • Mood disorders • Intellectual disability

Abbreviations

AD	Alzheimer's disease
CSF	Cerebrospinal fluid
$H_{1–4}R$	Histamine 1–4 receptors
HDC	L-Histidine decarboxylase
HMT	Histamine *N*-methyltransferase
mRNA	Messenger RNA
PD	Parkinson's disease
t-MeHA	Tele-Methylhistamine
TMN	Tuberomamillary nucleus

1 Introduction

In human genes, polymorphisms of monoamine-related neurotransmitter pathways, such as in the serotonin transporter genes, are highly associated with depression and anxiety disorders (Caspi et al. 2003; Homberg and van den Hove 2012; Shan et al. 2014). In addition, the dopaminergic neurons in the substantia nigra tend to be largely lost in Parkinson's disease (PD) (Hirsch et al. 1988). Effective treatments have been developed based upon these monoamine-related changes. For instance, selective serotonin reuptake inhibitors are widely prescribed for the treatment of

depression and anxiety-related disorders, and L-dopa was the first-line treatment for minimizing the motor symptoms of PD. Such pathophysiological relationships between monoamine and neuropsychiatric disorders are as yet unknown for the histamine neurotransmitter system, although fundamental studies have shown that the neuronal histaminergic system is involved in a number of physiological functions, such as the sleep-wake cycle, energy and endocrine homeostasis, sensory and motor functions, cognition and attention (Haas and Panula 2003; Haas et al. 2008; Panula and Nuutinen 2013; Shan et al. 2013b), which are all severely affected in neuropsychiatric disorders.

Recently a series of crucial data were obtained, demonstrating that the key enzyme for the production of neuronal histamine, histidine decarboxylase (HDC) was the cause of a rare familial case of Tourette syndrome (Ercan-Sencicek et al. 2010; Castellan Baldan et al. 2014) (details are reviewed in Pittenger 2017). In the light of the increasing interest in this topic, the time has come to integrate the scattered information on the pathophysiology of the histamine system in order to pave the way for novel therapeutic strategies. In this chapter, we bring together genetic association studies, neuroimaging reports, post-mortem human brain data, cerebral spinal fluid (CSF) measurement and the results of recent clinical trials to discuss the possible association of histamine receptors and key enzymes for histamine synthesis and metabolism with neuropsychiatric disorders.

2 Histamine Synthesis, Metabolism and Receptors in the Brain (Fig. 1)

Neuronal histamine is synthesised by HDC from the amino acid L-histidine, which is exclusively expressed in the tuberomamillary nucleus (TMN) (Fig. 2) of the mammalian brain (Panula and Nuutinen 2013). The enzyme histamine *N*-methyltransferase (HMT) inactivates histamine by transferring a methyl group from *S*-adenosyl-L-methionine to histamine. This is the only known pathway for the termination of histamine neurotransmission in the mammalian central nervous system. Histamine is known to have four types of receptors, all of which are G protein-coupled receptors. Histamine receptors 1–3 ($H_{1-3}R$) are functionally widely expressed in the brain. As several recent authoritative reviews (Passani and Blandina 2011; Schneider et al. 2014a, b; Panula et al. 2015) (for details see Shiroshi and Kobayashi 2017; Monczor et al. 2017; Schlicker and Kathmann 2017; Neumann 2017) have recently discussed the pharmacology, signal pathways and physiological function of histamine receptors we are not discussing these here. Recently accumulated evidence indicates that there is a new G protein-coupled histamine receptor, H_4R, which may also be functionally expressed in the brain (Connelly et al. 2009; Galeotti et al. 2013; Karlstedt et al. 2013). However, due to the controversial opinions regarding the lack of specificity of commercialized antibodies against H_4R (Beermann et al. 2012; Schneider and Seifert 2016) and inability of a H_4R agonist to initiate its downstream signal transduction in the cortex of various species (Feliszek et al. 2015), we will not further discuss this receptor.

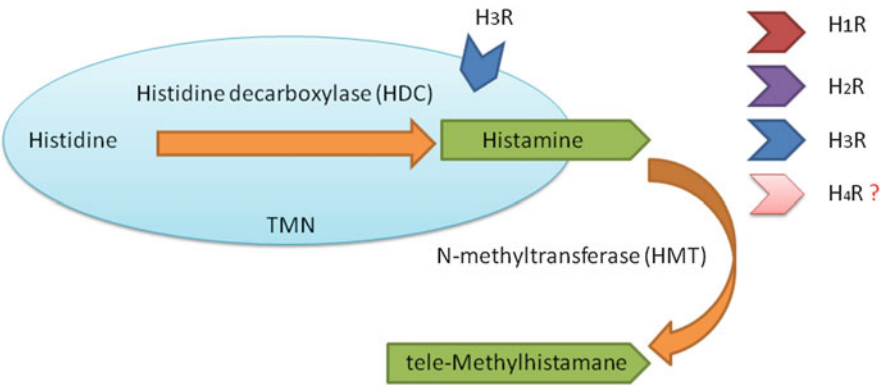

Fig. 1 Schematic illustration of histamine synthesis, metabolism and receptors. Histamine is synthesized by the specific enzyme histidine decarboxylase (HDC) in the tuberomamillary nucleus (TMN). The enzyme histamine *N*-methyltransferase (HMT) inactivates histamine. There are four types of histamine receptors ($H_{1-4}R$). H_3R is also an auto-receptor located pre-synaptically. The functional expression of H_4R in the brain is still unclear, which is indicated by a *question mark*

3 HDC

3.1 HDC Expression and Its Circadian Rhythmicity

Technically, the investigation of HDC is hampered by the fact that HDC-antibodies may also label other monoamine neurons in the substantia nigra, ventral tegmental area and dorsal raphe, by cross-reacting with aromatic L-amino acid decarboxylase (Mizuguchi et al. 1990). Therefore, we opted for in situ hybridization of HDC-messenger RNA (mRNA) for our studies. It should be noted, however, that the expression level of HDC-mRNA is low-to-moderate in post-mortem brain tissues (Liu et al. 2010). Consequently, appropriate specificity tests for both in situ probes and HDC-antibodies are always needed.

Circadian fluctuations of HDC-mRNA expression in the TMN have been reported, both in human (Shan et al. 2012c) and in rodent (Yu et al. 2014). In a group of neurodegenerative disorders, including AD, PD, preclinical PD and Huntington's disease, we observed a loss of this diurnal HDC-mRNA fluctuation (Shan et al. 2012c). These diseases showed symptoms of sleep-wake disturbance, which may, at least partly, be caused by alterations in the arousal-related TMN [reviewed in Lin (2000) and Shan et al. (2015b)]. It is therefore of interest to note that the circadian rhythm of HDC-mRNA expression and brain histamine levels were disturbed in mice that had knockdown of *BMAL1*, a key clock gene in the TMN neurons. These mice also showed functionally altered sleep architecture (Yu et al. 2014).

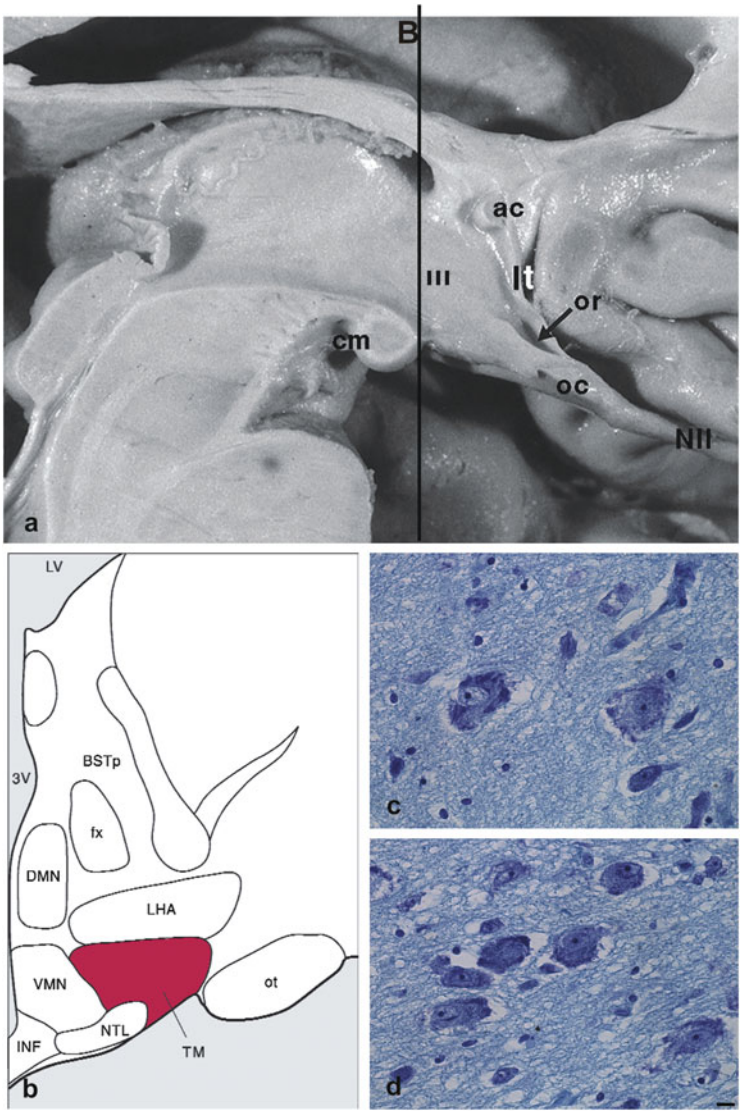

Fig. 2 The neuroanatomy of the tuberomamillary nucleus. (**a**) Medial surface of the human hypothalamus. Line *B* indicating the layer for figure (**b**). *Abbreviations*: *ac* anterior commissure, *cm* corpus mamillare, *lt* lamina terminalis, *NII* optic nerve, *oc* optic chiasm, *or* optic recess, *III* third ventricle. (**b**) The human hypothalamus in representative coronal cuts with the tuberomamillary nucleus highlighted (adapted from Fernandez-Guasti et al. 2000; Fig. 2). *Abbreviations*: *BSTp* bed nucleus of the stria terminalis posterior, *DMN* the dorsomedial hypothalamic nucleus, *OT* optic tract, *Ox* 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**, **d**) Examples of Nissl staining of TM nucleus neurons with typical neuron profiles, scale bar = 5 μm

3.2 Unaltered HDC Expression in Both PD and AD

During the preclinical and clinical PD stages, the HDC mRNA levels were fairly stable, indicating that neuronal histamine production remains intact (Shan et al. 2012d). The total number of histaminergic neurons (Nakamura et al. 1996) and the enzymatic activity of HDC (Garbarg et al. 1983) were also found to be stable in PD patients. The stability is further supported by the unaltered cerebrospinal fluid (CSF) level of the main metabolite of histamine, tele-Methylhistamane (t-MeHA), in PD patients (Prell et al. 1991). We have also observed that, in AD patients, despite the significant loss of histaminergic neurons, the TMN function may be largely compensated by the enhanced histamine production by the remaining histamine neurons, as indicated by the, largely, unaltered HDC-mRNA expression in the TMN (Shan et al. 2012b). The unchanged t-MeHA levels in the CSF of AD patients support this possibility (Motawaj et al. 2010).

3.3 Strong Increase in HDC Immuno-Reactivity in Narcoleptic Patients with Cataplexy: Is It Related to Hallucinations?

The significant loss of hypocretin (orexin) neurons in the hypothalamus is the major cause of narcolepsy with cataplexy (Peyron et al. 2000; Thannickal et al. 2000), which is characterized by clinical symptoms such as excessive daytime sleepiness, hypnagogic/hypnopompic hallucinations, sleep paralysis and disturbed nocturnal sleep (Overeem et al. 2001). Hypnagogic hallucinations occur during the transition from wakefulness to sleep, and hypnopompic hallucinations during the transition between sleep and consciousness.

Some clinical observations have shown that up to 65% of patients suffering from this disorder experienced hallucinations (Fortuyn et al. 2009; Leu-Semenescu et al. 2011). In fact, the symptoms of hypnagogic/hypnopompic hallucinations are so intense in some narcoleptic patients that they may lead to the misdiagnosis of schizophrenia (Douglass et al. 1991, 1993; Howland 1997; Talih 2011). This may also explain that comorbidity of narcolepsy and schizophrenia was often reported (Canellas et al. 2014; Chen et al. 2014; Plazzi et al. 2015). Narcoleptic animal models are generally generated based exclusively upon disturbed hypocretin (orexin) pathways. The major clinical symptoms can be found in these animal models, such as a short onset of rapid eye movement, cataplexy and fragmented sleep during the sleep stages (Chemelli et al. 1999; Hara et al. 2001; Tabuchi et al. 2014; Shan et al. 2015a). However, there is no way of telling whether these animals may have hallucinations. In 2013, two research groups independently observed that HDC immuno-reactivity is greatly increased in the TMN of narcoleptic patients (John et al. 2013; Valko et al. 2013), which indicates that not only the hypocretin (orexin) system, but also other systems, such as the histaminergic system, may be involved in narcolepsy. It should be noted that none of the narcoleptic animal models showed this HDC-neuropathology (John et al. 2013). It may be speculated that the strong increase in the number of histamine neurons may, at least partly, contribute to hallucinations found in narcolepsy. This possibility is supported by the

observation that patients with Huntington's disease, a disease that is reported to be accompanied by schizophrenia-like symptoms such as delusions and hallucinations (Tsuang et al. 1998, 2000; Correa et al. 2006), also had a significantly increased histamine production in the TMN (van Wamelen et al. 2011).

4 Histamine *N*-Methyltransferase (HMT)

4.1 HMT Mutations and Intellectual Disability

Recently, two homozygous *HMT* mutations (i.e. p.Gly60Asp and p.Leu208Pro) were identified in patients suffering from non-syndromic autosomal recessive intellectual disability in two unrelated consanguineous families of Turkish and Kurdish ancestry (Heidari et al. 2015). The patients from both families did not present with congenital malformations, facial dysmorphisms, neurological abnormalities or autistic features.

Subsequently, an in vitro study showed that, although the p.Gly60Asp mutation does not affect HMT expression at the mRNA or protein level, the enzymatic activity of HMT, the thermal stability and the affinity of binding to *S*-adenosyl-L-methionine were disrupted by a p.Gly60Asp mutation (Heidari et al. 2015). The p.Leu208Pro mutation was found to result in misfolding and rapid degradation of HMT protein (Heidari et al. 2015). Subsequent molecular dynamic simulations showed that the p.Leu208Pro mutation perturbs the helical character and disrupts the interaction with the adjacent β-strand, which is involved in the binding and correct positioning of histamine (Tongsook et al. 2016). This novel finding calls for detailed behaviour characterization of HMT knockout animals.

4.2 HMT in PD

Animal experiments have shown that increased histamine levels in the substantia nigra may cause a degeneration of dopaminergic neurons (Vizuete et al. 2000; Liu et al. 2007). HMT, the brain's main degradation enzyme for histamine, may thus play an important role in the pathogenesis of PD, but human studies do not support such a relationship.

A polymorphism of the *HMT* gene, rs11558538, causes the amino acid substitution Thr105Ile and leads to the formation of misfolded HMT protein, which is cleared by proteasomes, and therefore to a decreased HMT enzymatic activity (Pang et al. 2001). Individuals who are heterozygous for the 105Ile allele have 30–50% lower HMT activity, while individuals who are homozygous for the 105Ile have decreased enzyme activity of around 60% (Preuss et al. 1998; Horton et al. 2001; Rutherford et al. 2008). Several previous studies have revealed that the lower HMT activity alleles protect against PD development (Agundez et al. 2008; Ledesma et al. 2008; Palada et al. 2012; Yang et al. 2015). A recent meta-analysis, based upon five available studies involving 2,108 patients with PD and 2,158

controls, confirmed that decreased histamine metabolism in the central nervous system could play a role in protecting against PD (Jimenez-Jimenez et al. 2016).

In addition, there are a number of post-mortem studies that do not point to a protective role of HMT against the pathogenesis of PD. A significantly higher concentration of histamine – but not of t-MeHA (Rinne et al. 2002) – and accumulated histaminergic fibres (Anichtchik et al. 2000) was found in the substantia nigra, caudate nucleus and putamen of PD patients. Moreover, we reported an augmented HMT-mRNA expression in the same brain regions in PD patients (Shan et al. 2012a). It is as yet not clear whether the up-regulation of HMT-mRNA is induced by the increased levels of local histamine, but HMT does not appear to play a protective role in the inactivation of histamine, as the levels of t-MeHA remained unaltered (Rinne et al. 2002). Moreover, we also observed a negative correlation between HMT-mRNA expression in the substantia nigra and the disease duration of PD patients (Shan et al. 2012a). This suggested that the more serious (and thus the shorter lasting) the disease, the more HMT-mRNA is expressed. Based upon all these data, one could propose that the process of translation from mRNA to functional enzyme may be impaired in the basal ganglia of PD patients.

4.3 HMT Expression in Cerebral Cortex Related to Cognition and Mood State

As we discussed previously, the functional up-regulation of the histaminergic system in Huntington's patients may be involved in the cognitive impairment of this disease. An up-regulation of HMT-mRNA was also found in the inferior frontal gyrus of Huntington's disease patients (van Wamelen et al. 2011). In addition, increased histamine production as reflected by the HDC-mRNA expression (van Wamelen et al. 2011) and elevated CSF levels of histamine metabolites (Prell and Green 1991) were both reported in Huntington's disease.

Altered metabolic activity in the anterior cingulate cortex (ACC) has been consistently reported in the induction of the depressive state in major depressive disorders, and ACC metabolism and connectivity were found to be reversed by pharmacological treatment (Mayberg et al. 2000) or deep brain stimulation (Mayberg et al. 2005), which successfully improved the symptoms of depression (Kennedy et al. 2011). The lower HMT-mRNA expression in the ACC of depression patients (Shan et al. 2013a) may imply histamine level/turnover alterations in this pivotal brain region. This is in line with a reduction of the H_1R binding in the same brain region (Kano et al. 2004).

5 H_1R

5.1 Modulation of Cognition and Mood

A reduction of H_1R binding was reported in several neuropsychiatric disorders. Positron emission tomography studies showed that H_1R binding, detected by the radioligand for H_1R, ^{11}C-doxepin, was much lower in the frontal cerebral cortex of

depressive patients compared to matched controls (Kano et al. 2004; Yanai and Tashiro 2007). Interestingly, H_1R binding in the frontal cortex and cingulate gyrus decreased in relation to self-rated depressive scale scores (Kano et al. 2004). It was also reported that the amount of H_1R binding is reduced in the frontal and temporal brain areas of AD patients (Higuchi et al. 2000). More importantly, there is a correlation between H_1R binding and severity of cognitive symptoms (Higuchi et al. 2000).This alteration seems to be specifically receptor-dependent, because the binding of another histamine receptor, H_2R, was unchanged in AD prefrontal cortex (Perry et al. 1998). In a post-mortem study, the patients with chronic schizophrenia also showed a significant reduction in H_1R binding in the frontal cortex (Nakai et al. 1991).

Notably, a lack of changes in the H_1R-mRNA was observed in the frontal cortex in depression (Shan et al. 2013a) as well as in AD (Shan et al. 2012b) in our post-mortem studies. The possible deficits in the translation of H_1R-mRNA to the functional H_1R in the cortex in these disorders deserve future attention.

5.2 H_1R Antagonists as a Treatment for Insomnia

Many H_1R antagonists are able to cross the blood–brain barrier and cause drowsiness (Lieberman 2009). Diphenhydramine, chlorpheniramine, doxylamine and brompheniramine are over-the-counter medicines with H_1R antagonistic activity. They have been prescribed to treat allergies, cold symptoms, itching, nausea and insomnia (Krystal et al. 2013). It should be noted that some antidepressants and antipsychotics with a major effect on cholinergic, dopaminergic, serotoninergic and adrenergic receptors may also act on histamine-related mechanisms that show beneficial effects on insomnia (Krystal 2009).

A placebo-controlled trial using the selective H_1R antagonist doxepin in patients with chronic primary insomnia (Roth et al. 2007) showed a major effect in terms of preventing early morning awakening, as well as in terms of improved sleep in the second part of the night.

6 H_2R and Schizophrenia

An early study demonstrated that schizophrenic patients had a higher incidence of the H2R649G allele polymorphisms located in the coding region of the H_2R gene (Orange et al. 1996). However, a follow-up study with a larger sample size did not support this association of the allelic variation with schizophrenia (Ito et al. 2000). In early preliminary open-label clinical trials, the H_2R-antagonist famotidine was shown to have an antipsychotic effect and to reduce negative schizophrenic symptoms (Kaminsky et al. 1990; Oyewumi et al. 1994; Rosse et al. 1996). The antipsychotic effects of famotidine were confirmed in a recent randomized clinical trial. Obvious improvements in both positive and negative symptoms of schizophrenia patients were obtained in that study (Meskanen et al. 2013). The authors of

this study pointed out that famotidine treatment requires high dosage because of its low blood–brain barrier penetration. However, a meta-analysis that pooled eight double-blind randomized placebo-controlled trials with the H_2R-antagonists (famotidine, nizatidine or ranitidine) as adjunctive therapy did not observe any effect on schizophrenic symptoms (Kishi and Iwata 2015).

7 H_3R

7.1 Treatment of Alzheimer's Disease and Schizophrenia

Various ongoing clinical trials study the use of H_3R-antagonist/inverse agonist for the treatment of AD, PD, narcolepsy, schizophrenia and attention-deficit hyperactivity disorder (Brioni et al. 2011; Passani and Blandina 2011). The neurobiological basis of this application is that H_3R-antagonists/inverse agonists stimulate the release of histamine, GABA, acetylcholine and dopamine in the brain (Medhurst et al. 2007; Galici et al. 2009; Giannoni et al. 2010). However, no beneficial effects emerged in terms of improving cognitive functioning in the application of H_3R-antagonists/inverse agonist for the treatment of AD or mild-to-moderate AD patients (Egan et al. 2012, Grove et al. 2014, Kubo et al. 2015). On the other hand, this is in line with the small increase in H_3R-mRNA we observed in female AD patients (Shan et al. 2012b), together with the insignificant changes of H_3R-binding density in the prefrontal cortex reported by another post-mortem study (Medhurst et al. 2007). To date, H_3R inverse agonists also failed to show a therapeutic effect in schizophrenia (Egan et al. 2013, Haig et al. 2014, Jarskog et al. 2015).

7.2 Treatment for Hypersomnia

It is noted, however, that preclinical and clinical data indicate the positive effectiveness of H_3R-antagonist/inverse agonist for the treatment of daytime sleepiness in several neurological disorders associated with hypersomnia (Passani and Blandina 2011). In a narcolepsy animal model, i.e. the hypocretin (orexin)-knockout mice, the administration of Pitolisant yielded significant improvement of the key symptoms of sleepiness, and it decreased direct onsets of rapid eye movement sleep from wakefulness, which is a diagnostic criterion for narcolepsy (Lin et al. 2008). In both adults and children with narcolepsy, Pitolisant ameliorated excessive daytime sleepiness (Lin et al. 2008; Inocente et al. 2012; Dauvilliers et al. 2013). Pitolisant has, therefore, been approved as orphan drug for narcolepsy.

To date, only few published reports document the treatment effects of H_3R-antagonist/inverse agonist on excessive sleepiness in PD, but various clinical trials are still ongoing [according to the clinical trial data base (https://clinicaltrials.gov)].

8 Conclusion and Perspective

Recent data indicate that alterations in several components of the histaminergic system may contribute to the pathogenesis of neuropsychiatric disorders such as narcolepsy, schizophrenia, depression, AD and PD (Table 1). The histaminergic compounds were shown to have novel therapeutic applications. The increased number of histamine neurons (marked by HDC) in the narcoleptic brain is hypothesized to contribute to the hypnagogic/hypnopompic hallucinations of this disorder. HMT was presumed to play a role in the pathogenesis of PD, but the animal data and human genetic, post-mortem studies failed to show a consistent effect. In addition, two rare *HMT* gene mutations were found to lead to intellectual disability. They deserve to be studied in HMT knockout animal model. A reduction of H_1R binding in the cerebral cortex was observed in AD, depression and schizophrenia, which may imply that H_1R availability is associated with cognitive functions and mood states. The H_1R knockout animal seems to provide a great opportunity for further studies of such an involvement in cognition and anxiety. H_1R antagonists are a potential effective treatment for insomnia. Preliminary results have shown that the H_2R-antagonist induced a significant improvement of schizophrenic symptoms. Novel antagonists with higher penetration rate through the blood–brain barrier and follow-ups in clinical trials are urgently needed. One of the H_3R-antagonist/inverse agonists, Pitolisant, has been approved for clinical treatment for narcolepsy. The effectiveness of other H_3R-antagonist/inverse agonist for the treatment of excessive daytime sleepiness has to be studied in animal models and clinical trials. The functional expression of H_4R is not yet clear. However, recently an anxiety and

Table 1 Overview of key alterations of brain histaminergic system in neuropsychiatric disorders

	Histamine production		
Disorders	TMN neurons	HDC-mRNA	Key changes of histamine metabolism and receptors in brain areas
PD	–	–	SN (mRNA HMT ↑; H_3R ↓, HA level ↑; H_3R binding ↑) PU mRNA (HMT ↑; H_3R↓;H_4R ↑;HA level ↑), t-MeHA level in CSF–
AD	↓(−57%)	–/↓(−20%)	PFC mRNA (HMT and H_3R ↑), HA level in brain↑/↓ in CSF–/↑/↓
Huntington's disease	–	↑(+63%)	IFG mRNA (H_1R ↑; H_3R ↑; HMT ↑);CN mRNA (H_2R↓; H_3R↓), H_2R and H_3R binding ↓. H_1R binding ↑, t-MeHA in CSF↑
Depression	–	–	ACC mRNA (HMT↑);H_1R binding by PET scanning ↓in ACC and PFC
Narcolepsy	64 or 94%↑	N.A.	HA level in CSF–/↓, t-MeHA level in CSF–

Notes and Abbreviations: ↑ increase, – unaltered, ↓ decrease, *CSF* cerebrospinal fluid, *CN* Caudate nucleus, *HDC* histidine decarboxylase, *HMT* histamine methyltransferase, *LB*, *LN* Lewy bodies, Lewy neurites, *PU* putamen, *PFC* prefrontal cortex, *IFG* Inferior frontal gyrus, *SN* substantia nigra, *TMN* tuberomamillary nucleus, *NFT* neurofibrillary tangles, *$H_{1-4}R$* histamine-1-4-receptor, *t-MeHA* tele-melthyhistamine

despair behavioural phenotype of a histamine H_4R knockout mice has been identified by the use of a light–dark box and the tail suspension test (Sanna et al. 2017). The possible role of this novel histamine receptor in the central nervous system deserves further research in both animal models and patients with neuropsychiatric disorders.

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Conflicts of Interest: We declare that we have no conflicts of interest.

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