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Invited review

# Histamine and histamine receptors in Tourette syndrome and other neuropsychiatric conditions

Maximiliano Rapanelli [a], Christopher Pittenger [a, b, c, d, *]

[a] Department of Psychiatry, Yale University, New Haven, CT, USA
[b] Department of Psychology, Yale University, New Haven, CT, USA
[c] Department of Child Study Center, Yale University, New Haven, CT, USA
[d] Department of Interdepartmental Neuroscience Program, Yale University, New Haven, CT, USA

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ABSTRACT

The potential contributions of dysregulation of the brain's histaminergic modulatory system to neuropsychiatric disease, and the potential of histamine-targeting medications as therapeutic agents, are gradually coming into focus. The H3R receptor, which is expressed primarily in the central nervous system, is a promising pharmacotherapeutic target. Recent evidence for a contribution of histamine dysregulation to Tourette syndrome and tic disorders is particularly strong; although specific mutations in histamine-associated genes are rare, they have led to informative studies in animal models that may pave the way for therapeutic advances. A controlled study of an H3R antagonist in Tourette syndrome is ongoing. Preclinical studies of H3R antagonists in schizophrenia, attention deficit disorder, and narcolepsy have all shown promise. Recently reported controlled studies have been disappointing in schizophrenia and attention deficit disorder, but the H3R antagonist pitolisant shows promise in the treatment of narcolepsy and excessive daytime sleepiness and is currently under regulatory review for these conditions.



## 1. Introduction

The brain's histaminergic (HA) modulatory system has received less attention as a locus of pathology and potential therapeutic target than the monoaminergic systems (Haas et al., 2008; Panula and Nuutinen, 2013). However, its anatomical organization has much in common with the more extensively studied dopaminergic, serotonergic, and noradrenergic systems. Histaminergic neurons are clustered in the posterior hypothalamus, from which they project broadly throughout the central nervous system. Acting on four G-protein coupled receptors, H1R–H4R, they have diverse modulatory effects throughout the brain. Given this capacity for widespread modulation of neuronal information processing, alterations in HA neurotransmission are likely to contribute to disruptions in brain function and thus to neuropsychiatric disease.

There has long been interest in brain histamine receptors, especially the H3 receptor, as potential therapeutic targets (Sander et al., 2008; Schwartz, 2011). In recent years the role of HA dysregulation as a pathophysiological contributor to a range of illnesses has begun to come into sharper focus (Ercan-Sencicek et al., 2010; Shan et al., 2015a). Importantly, these two lines of work need not converge – histaminergic modulation may prove to be therapeutically useful even in conditions in which HA dysregulation is not central to pathophysiology. H3 antagonists are particularly promising in the treatment of narcolepsy and extensive daytime sleepiness, as reviewed below; investigations are ongoing in a range of other conditions. This remains an area of rapid development and significant therapeutic promise.

In this review we summarize recent literature on the role of HA dysregulation in neuropsychiatric disease and discuss a range of studies in which therapeutic modulation of histaminergic receptors has been attempted. We focus in most detail on tic disorders and Tourette syndrome, in which recent genetic studies and work in animal models have implicated dysregulated histaminergic neurotransmission as a rare but informative contributor to pathophysiology. Other specific conditions in which histamine interacts with pathophysiological processes, including the pathophysiology of Alzheimer's disease and modulation of dopamine in the nucleus accumbens, are covered in detail elsewhere in this issue.

* Corresponding author. 34 Park Street, W315, New Haven, CT 06519, USA.
*E-mail address:* Christopher.pittenger@yale.edu (C. Pittenger).

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## 2. Dysregulation in histamine signaling in Tourette syndrome

Motor and vocal tics occur in approximately 5% of the population; Tourette syndrome represents the most severe end of a spectrum of tic disorders and affects ~0.3–1.0% (Scahill et al., 2013). Many cases improve with age, but severe cases can persist and cause profound morbidity (Bloch et al., 2013). Available therapies are of limited efficacy and are often limited by side effects (Bloch, 2008; Eddy et al., 2011).

A landmark genetic study in 2010 identified a rare, dominant-acting mutation in the histidine decarboxylase (*Hdc*) gene, which encodes the enzyme required for the conversion of histidine into histamine, as a putative cause of Tourette syndrome in a single family with an exceptionally high incidence of the disorder (Ercan-Sencicek et al., 2010). This represents the first time that abnormalities in histaminergic neurotransmission have been clearly implicated as causative in any neuropsychiatric condition. The implicated nonsense mutation truncates the protein and produces a mutant enzyme that is unable to convert histidine into histamine; *in vitro*, it functions as a dominant negative, interfering with the ability of wild-type protein to produce histamine (Ercan-Sencicek et al., 2010).

This mutation is, thus far, unique to the index family. However, subsequent genetic studies have provided evidence that other abnormalities in histaminergic signaling may also increase risk for TS. A candidate gene study by Karagiannidis and colleagues examined polymorphisms in the *Hdc* gene and found overtransmission of two single nucleotide polymorphisms (SNPs) and the associated haplotypes in TS patients (Karagiannidis et al., 2013). While candidate gene studies have a poor track record in neuropsychiatric disease and such findings should thus be treated with caution (Fernandez et al., 2015), this finding, if replicated, suggests that common polymorphisms, not just the high-penetrance but rare mutation described initially, can contribute to TS risk in the population. A recent study of copy number variation (CNVs) provide further support for abnormalities in HA signaling in TS patients beyond the original family (Fernandez et al., 2012). Importantly, it was not the *Hdc* gene itself that was implicated by this CNV study, but rather signaling through the H1R and H2R pathways. While further studies in larger cohorts of patients are needed, this CNV study provides convergent evidence for dysregulation of histaminergic signaling as an important causal factor in at least some cases of TS.

## 3. The HDC knockout mouse as a pathophysiological model of TS

The implication of a hypomorphic allele of the *Hdc* gene as a rare cause of TS (Ercan-Sencicek et al., 2010) created a rare opportunity for the generation of a pathophysiologically grounded model of the disorder. Modeling pathophysiology of TS, like other genetically complex neuropsychiatric diseases, has been challenging (Pittenger, 2014). Even the largest GWAS studies reported to date have produced no confirmed disease-associated alleles (Fernandez et al., 2015; Scharf et al., 2013); and common disease-associated alleles tend to be of small effect size and therefore of limited utility in grounding informative animal models. Though it is rare, the *Hdc* mutation is of large effect size; every known carrier has TS. Furthermore, it has a well-defined biochemical effect – abrogation of the biosynthetic capacity of the enzyme – that can readily be assayed *in vitro* or *in vivo*.

Capitalizing on these characteristics, our laboratory has focused on the *Hdc* knockout mouse as a potentially informative model of TS with unique etiologic validity (Castellan Baldan et al., 2014). This knockout mouse was developed over a decade ago (Ohtsu et al., 2001) and has been studied in a variety of contexts (Ohtsu et al., 2001; Abe et al., 2004; Acevedo et al., 2006a, 2006b; Anaclet et al., 2009; Brabant et al., 2007; Chepkova et al., 2012; Dere et al., 2004; Dere et al., 2003; Fitzsimons et al., 2001; Gong et al., 2010; Gong et al., 2010; Kubota et al., 2002; Lin et al., 2008; Liu et al., 2007; Parmentier et al., 2002; Schneider et al., 2014), but its potential as a model of TS did not become clear until the genetic discoveries described above (Ercan-Sencicek et al., 2010; Fernandez et al., 2012). *Hdc* knockout mice, backcrossed extensively onto C57Bl/6, have undetectable brain HA (Castellan Baldan et al., 2014). Past studies have found no marked alterations in whole-tissue DA or its metabolites in these mice (Dere et al., 2003; Kubota et al., 2002); however, they have elevated DA turnover (Dere et al., 2003), and *in vivo* microdialysis reveals modestly but significantly elevated extracellular dopamine (DA) in the striatum (Castellan Baldan et al., 2014; Rapanelli et al., 2014), the primary input nucleus of the basal ganglia and a structure repeatedly implicated in the pathophysiology of TS (Williams et al., 2013). The knockout mice have been shown to be more active after either acute or chronic treatment with the psychostimulant methamphetamine (Kubota et al., 2002).

HDC knockout mice do not exhibit detectable tic-like movements at baseline. However, when challenged with either high-dose psychostimulants or acute stress they develop repetitive purposeless movements – stereotypy or excess grooming – that may recapitulate the tics that are pathognomonic of TS (Castellan Baldan et al., 2014; Xu et al., 2015). Knockout mice also have a deficit in prepulse inhibition, a measure of sensorimotor gating that is impaired in patients with tics – including, importantly, the carriers of the *Hdc* mutation (Castellan Baldan et al., 2014). No animal model can recapitulate all aspects of the complex phenomenology of TS (Pittenger, 2014) – the lack of spontaneous tics is a particular point of divergence from what is observed in patients. Nevertheless, these behavioral phenotypes suggest that the *Hdc* knockout mouse is successfully reproducing key aspects of the disorder and is therefore a valid model for further investigations into pathophysiology.

Abnormalities of dopaminergic regulation of the basal ganglia have long been implicated in TS (Williams et al., 2013; Denys et al., 2013); as noted above, the *Hdc* knockout mouse has elevated extracellular DA, as measured by microdialysis, in the striatum (Castellan Baldan et al., 2014; Rapanelli et al., 2014). This motivated an investigation of dopamine receptors throughout the basal ganglia in TS patients who carry the *Hdc* mutation, using PET imaging with the D2R/D3R agonist ligand $^{11}$C–PHNO. Receptor levels were not detectably altered in the striatum, where PHNO binding primarily reflects D2R levels, but they were elevated in the substantia nigra, where D3R predominates. Importantly, this increased receptor binding is also seen in the *Hdc* knockout mouse, assayed *ex vivo* using the D2R/D3R ligand raclopride (Castellan Baldan et al., 2014). Molecular signaling pathways known to be regulated by DA in the striatum are complexly dysregulated in the *Hdc* KO mice (Rapanelli et al., 2014). Further characterization of these abnormalities has the potential to identify new candidate mechanisms for TS and new molecular targets for intervention.

Histamine H2 and H3 receptor expression is altered in the brain of *Hdc* mice (Chepkova et al., 2012; Fitzsimons et al., 2001). Because these mice lack HA, expression of HA receptors might be thought to be irrelevant. This is not the case in *Hdc* heterozygotes, however, or in patients with a heterozygous abnormality in the *Hdc* gene (Ercan-Sencicek et al., 2010) or in some other component of histaminergic signaling (Fernandez et al., 2012). Furthermore, developing insights into the function of the H3R histamine receptor, described elsewhere in this volume (CITE ARIAS-MONTANO, THIS VOLUME), suggest its potential to influence cellular events even in the absence of HA. H3R expression is restricted to the central nervous system. It is a G-protein-coupled receptor that is typically

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