Received: 24 September 2018 | Revised: 12 December 2018 | Accepted: 7 January 2019

DOI: 10.1111/bph.14606

Themed Section: New Uses for 21st Century

REVIEW ARTICLE

The histidine decarboxylase model of tic pathophysiology: a new focus on the histamine H_3 receptor

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Funding information
National Institute of Mental Health, Grant/Award Number: R21MH109700

Histamine dysregulation was implicated as a rare cause of Tourette syndrome and other tic disorders a decade ago by a landmark genetic study in a high density family pedigree, which implicated a hypomorphic mutation in the *histidine decarboxylase* (*Hdc*) gene as a rare but high penetrance genetic cause. Studies in *Hdc* knockout (KO) mice have confirmed that this mutation causes tic-relevant behavioural and neurochemical abnormalities that parallel what is seen in patients and thus validate the KO as a potentially informative model of tic pathophysiology. Recent studies have focused on the potential role of the histamine H_3 receptor in this model, and by association in tic disorders and related neuropsychiatric conditions. The H_3 receptor is up-regulated in the striatum in *Hdc* KO mice. As the H_3 receptor has constitutive activity in the absence of ligand, this receptor up-regulation may have significant cellular effects despite the absence of neurotransmitter histamine in these mice. Activation in vivo of H_3 receptors in wild type mice regulates signalling in striatal medium spiny neurons (MSNs) that interacts non-linearly with dopamine receptor signalling. Baseline signalling alterations in MSNs in *Hdc* KO mice resemble those seen after H_3 receptor agonist treatment in wild type animals. H_3 receptor agonist treatment in the KOs further accentuates most of these signalling abnormalities and produces behavioural stereotypy. Together, these data suggest the intriguing hypothesis that constitutive signalling by up-regulated H_3 receptors explains many of the molecular and behavioural abnormalities seen in these animals.

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1 | INTRODUCTION: HISTAMINE ABNORMALITIES IN TIC DISORDERS

Histamine has been recognised as having an important role as a modulatory neurotransmitter since the 1980s, when histaminergic neurons were first identified in the posterior hypothalamus (Panula, Yang, & Costa, 1984). Subsequent studies have shown histaminergic neurons to project widely throughout the brain and to exert a range of modulatory functions via three **receptors**, **H_1**, **H_2** and **H_3** (Haas, Sergeeva, & Selbach, 2008; Panula & Nuutinen, 2013). A fourth receptor, **H_4**, is mostly found peripherally, and whether it has direct effects in the CNS remains a topic of some controversy. Histamine receptors are prominently expressed in the basal ganglia (Haas et al., 2008; Pillot et al., 2002; Vizuete et al., 1997), where they have a range of molecular and electrophysiological effects (Ellender, Huerta-Ocampo,

Abbreviations: ADHD, attention deficit hyperactivity disorder; DARPP-32, dopamine and cAMP-regulated phosphoprotein, 32 kDa; dMSN, medium spiny neuron of the direct pathway (expressing D_1 receptors); Hdc, Histidine decarboxylase; iMSN, medium spiny neuron of the indirect pathway (expressingD_2 receptors); MSN, medium spiny neuron; OCD, obsessive–compulsive disorder; PPI, prepulse inhibition; RAMH, R-α-methyl-histamine; rpS6, ribosomal protein 6; SNP, single nucleotide polymorphism; TS, Tourette syndrome

Deisseroth, Capogna, & Bolam, 2011; Moreno et al., 2011; Alfaro-Rodriguez et al., 2013; Moreno et al., 2014; Rapanelli et al., 2016; Rapanelli, Frick, Pogorelov, et al., 2017).

There have been many investigations into the association of histamine dysregulation with neuropsychiatric disease over the years. For example, the H_1 receptor can regulate alertness, and alterations in histaminergic neurons have been associated with narcolepsy in some studies (John et al., 2013; Valko et al., 2013). Abnormalities of histaminergic signalling have been reported in post-mortem studies of individuals with neurodegenerative disease (Shan, Bao, & Swaab, 2015) and, more recently, in autism (Wright et al., 2017). However, in these cases, and others that could be listed, it is unclear whether histamine dysregulation is a cause, a correlate, or a consequence of core pathophysiological processes.

The hypothesis that histamine deficiency can lead to Tourette syndrome (TS), other tic disorders, and related conditions derives from a seminal genetic observation a decade ago. A rare nonsense mutation in the gene for **histidine decarboxylase** *(Hdc)*, which encodes the enzyme essential for histamine production, was associated with tics in a two-generation pedigree with an exceptionally high frequency of TS, along with a somewhat lower frequency of comorbidities such as obsessive–compulsive disorder (OCD), autism, and attention deficit hyperactivity disorder (ADHD; Ercan-Sencicek et al., 2010). Subsequent genetic studies have provided evidence that abnormalities in histamine signalling may contribute to tic disorders beyond this single family (Fernandez et al., 2012; Karagiannidis et al., 2013). Such genetic associations imply a causal role for dysregulated histamine signalling, not just a correlation, in tic disorders. This has motivated a new focus on how disruption of histaminergic neurotransmission can produce TS-relevant phenomenology.

We have characterized the *Hdc* knockout (KO) mouse as a potential model of the pathophysiology of tics (Pittenger, 2017a). These mice exhibit behavioural, neurochemical, and neurobiological abnormalities that parallel core characteristics of TS (Castellan Baldan et al., 2014), validating them as a promising model that may reveal novel pathophysiological principles. Here, we briefly review initial work in this model, which has recently been described in more detail elsewhere (Pittenger, 2017a), and then focus more specifically on recent data suggesting that dysregulation of the H_3 receptor in the basal ganglia contributes to the tic-relevant phenomenology in these mice (Rapanelli, Frick, Pogorelov, et al., 2017). The H_3 receptor thus emerges as an interesting focus of pathophysiology and a potential therapeutic target in tic disorders and related conditions.

2 | CLINICAL FEATURES AND NEUROBIOLOGY OF TIC DISORDERS

Tics consist of brief, non-rhythmic, semi-voluntary movements, often performed to discharge a build-up of localized discomfort or tension, much as a sneeze discharges a build-up of discomfort in the back of the nose. Approximately 20% of children develop tics; they are more common in males than in females (Robertson, Eapen, & Cavanna, 2009; Scharf, Miller, Mathews, & Ben-Shlomo, 2012). In many of these children, tics are mild and fluctuating; in mild cases, they may never be diagnosed, and they often do not require treatment. Tics often improve spontaneously as children age, and thus, they are less common in adults. A diagnosis of TS is given when both motor and vocal tics are present and are persistent; it is unclear whether TS represents a distinct pathophysiological entity or just one end of a spectrum of tic disorders. Tics typically fluctuate, in both TS and tic disorders more generally, and they can be exacerbated by stress and sleep deprivation (Du et al., 2010; Leckman, 2002).

Our understanding of the pathophysiology of TS remains limited, but certain principles are generally recognized and can help guide interpretation of genetic studies and investigations in animal models (Pittenger, 2017b). Convergent findings from structural and functional imaging studies have implicated dysregulated activity in the corticostriatal circuitry, particularly the caudate and putamen (collectively known as the striatum) and the afferent supplementary motor area. The striatum is reduced in size in individuals with TS (Peterson et al., 2003), and localized cellular pathology has been reported in post-mortem studies (Kalanithi et al., 2005; Kataoka et al., 2010; Lennington et al., 2016).

Within the corticostriatal circuitry, dysregulation of the modulatory neurotransmitter **dopamine** has been reported in neuroimaging studies (Denys et al., 2013; Singer et al., 1992; Wong et al., 2008) and in a number of pathophysiological investigations in animals (Pittenger, 2017b). Psychostimulant drugs, which elevate dopamine release in the striatum, can trigger or exacerbate tics in patients if used at high doses (Denys et al., 2013; Feinberg & Carroll, 1979), and dopamine receptor antagonists represent the most effective pharmacotherapy for tics (Bloch, 2008).

Because of these observations in patients, there are reasonable a priori expectations that valid models of the pathophysiology of tic disorders will exhibit abnormalities in the corticostriatal circuitry, especially dysregulated neuronal activity and altered dopamine dynamics. These expectations have guided early analysis of the *Hdc* model.

3 | *Hdc* MUTATIONS IN TS

It has long been appreciated that tic disorders are significantly genetic; heritability has been estimated at approximately 50% (Fernandez, State, & Pittenger, 2018). However, as is the case in other complex neuropsychiatric conditions, mutations in many different genes are thought to contribute and to interact with each other and with environmental and developmental factors in complex ways that are not well understood. Clarity as to genetic contributors to disease has thus been slow to emerge, despite decades of effort (Fernandez et al., 2018). An initial genome-wide association study supported the notion that common variants with individually small effect sizes contribute to the pathogenesis of tics, but it did not unambiguously implicate any specific genetic contributors (Scharf et al., 2013).

Secondary analysis of these genome-wide association study data suggested that rare genetic variants may contribute substantially to tics (Davis et al., 2013). The identification of very rare genetic variants with individually large effect sizes has particular value in investigations of pathophysiology, because reproducing such mutations in model systems is more likely to reveal disease-associated downstream

effects than more common mutations of small effect size. The search for such rare but informative mutations has been particularly successful in the study of autism (Willsey & State, 2015); it has begun to bear fruit in investigations of TS (Fernandez et al., 2018; Willsey et al., 2017).

Ercan-Sencicek and colleagues studied a family with an exceptionally high incidence of TS (along with a high incidence of comorbid conditions such as OCD, ADHD, and autism). They identified a single genetic interval that segregated with tics; in the 51 genes within this interval, they found a single coding-frame mutation: a nonsense mutation, W317X, in exon 9 of *histidine decarboxylase* (Ercan-Sencicek et al., 2010). This unexpected finding was the first time that disrupted histamine biosynthesis was implicated in the pathophysiology of tics.

A few subsequent investigations provided further support to this association. In a study of copy number variants, large-scale alterations in genetic architecture that can affect many genes, Fernandez and colleagues found an over-representation of genes associated with histamine signalling (Fernandez et al., 2012). This result is powerful because it, like the original finding of Ercan-Sencicek et al. (2010), examined the whole genome without specifying any particular hypothesis. The fact that histamine dysregulation was independently implicated by these two data-driven studies increases confidence that the finding is real. Using a different, hypothesis-driven approach, Karagiannidis and colleagues specifically examined common genetic variants within the *Hdc* gene (Karagiannidis et al., 2013). They identified two single-nucleotide polymorphisms (SNPs) that are more common in individuals with TS than in controls. This suggests that common genetic variants in this gene can contribute to risk for tic disorders.

4 | THE POWER AND PERILS OF ANIMAL MODELS OF COMPLEX NEUROPSYCHIATRIC DISEASE

As noted above, rare mutations of large effect size—that is, in the extreme, monogenic causes of disease—are particularly valuable for the study of the pathophysiology of complex disease. It is important, however, to acknowledge the limitations of such modelling efforts, alongside their potential (Pittenger, 2014).

There are several impediments to the comprehensive modelling of complex human neuropsychiatric disease in mice or other model systems (Bortolato & Pittenger, 2017). First, biological differences between species may make it impossible to reproduce core characteristics across phylogenetic boundaries. For example, it is unlikely that the full phenomenology of dyslexia will ever be captured in a non-human model system, as defining symptomatology depends on the underlying capacity to read, which is (as far as we know) unique to humans. It may prove to be the case that important aspects of other neuropsychiatric conditions, such as thought disorder in psychosis, linguistic difficulty in autism, and suicidality in depression simply cannot be captured in other organisms. Whether this is true of TS is not obvious a priori. Certainly, other animals are capable of phasic, non-rhythmic, purposeless movements, but whether they can reproduce all aspects of tic phenomenology remains unclear (Pittenger, 2014).

A second difficulty is that even if key disease-related processes can be reproduced in an animal model, they may be difficult to unambiguously identify and quantify. For example, if non-human animals can develop thought disorder and other aspects of psychosis, how would we know, absent verbal report? In the case of tic disorders, what sort of phasic, nonrhythmic movements should be considered equivalent to tics? Is it best to look for all topographic characteristics of tics, as some have done (Bronfeld, Yael, Belelovsky, & Bar-Gad, 2013; McCairn, Bronfeld, Belelovsky, & Bar-Gad, 2009) or to take a broader view and be encouraged by less perfectly homomorphic behaviours such as elevated grooming or focused stereotypy (Bortolato & Pittenger, 2017)? This is not obvious from first principles.

A third challenge, particularly in the case of neuropsychiatric disease, is that the disease entities being modelled may themselves be fuzzy categories. It is unclear whether diagnoses that our current nomenclature suggests as being well-demarcated entities are instead clusters of conditions whose boundaries are yet to be delineated, arbitrary subsets of supraordinate categories, or portions of broader continua of symptomatology, without discrete boundaries. It is thus not always clear what entities might best be modelled in pathophysiology studies. In the case of tic disorders, should we be seeking to reproduce the pathophysiology of TS specifically, or of tic disorders in general, or of tics in combination with some or all of the common comorbidities (e.g., OCD, ADHD, and autism)?

It would be a mistake, however, to conclude from these difficulties that attempts to capture aspects of the pathophysiology of neuropsychiatric disease are fundamentally hopeless. Most of the genes, most of the properties of neurons and their interconnections, and most of the large-scale divisions of the brain are fairly well conserved across mammals. In the case of tic disorders, the implicated corticostriatal circuitry is phylogenetically ancient, and its interconnections are broadly similar between mice and humans. Studies of pathophysiology in mice therefore may shed light on parallel processes in humans, if carefully conducted and thoughtfully interpreted.

Several conclusions have informed our studies of the *Hdc* KO model. First, pathophysiological modelling is most powerful when it captures a hypothesized cause (or large-effect-size risk factor) that is unambiguously translatable from humans to mice. A rare mutation of large effect, such as the *Hdc* mutation described above (Ercan-Sencicek et al., 2010), is an ideal foundation. Second, when evaluating such a model, it is best to be agnostic as to precisely what form disease-relevant phenotypes may take; perfect replication of disease-relevant pathophysiology may not produce behavioural effects that perfectly mimic human symptoms, and thus one should cast a broad net (e.g., multiple forms of repetitive behaviour, along with tests of other symptomatology seen in tic disorders). It is also helpful to consider not only the symptomatology of the condition being modelled but also its temporal pattern and respond to modulating influences; in the case of tics, for example, modulation by stress, sleep deprivation, and psychostimulant challenge can be tested in an animal model.

Finally, initial validation of a model—that is, building a convincing case that reproducing a hypothesized cause produces disease-relevant effects—provides support for the motivating hypothesis, but it is only a first step. Because of the unavoidable differences between mice and humans, findings in any rodent model must always be considered provisional, and parallelism between the model and findings from patients must be sought whenever possible. The ultimate validation of a model lies in using it to generate novel hypotheses that are then validated in studies in humans. In the case of the *Hdc* KO mouse, to which we now turn, parallelism between the model and human carriers of the *Hdc* W317X mutation has been established at several levels (Castellan Baldan et al., 2014; Xu, Li, Ohtsu, & Pittenger, 2015). However, while the model has produced several novel testable hypotheses, as further discussed below, these have not yet been confirmed in studies of genetically heterogeneous tic patients. This final step in the translational enterprise is an important focus of ongoing work.

5 | THE *Hdc* KO MODEL: INITIAL VALIDATION AND STUDIES OF CIRCUIT PATHOPHYSIOLOGY

Mice with a null mutation in the *histidine decarboxylase* gene were generated nearly 20 years ago and had been used in studies of inflammation, sleep, and other topics before the genetic association with tics was discovered (Ohtsu, 2010; Ohtsu et al., 2001; Schneider, Neumann, & Seifert, 2014b). There has been some variation in reported behavioural phenotypes of these mice, in measures such as spontaneous exploratory activity and anxiety-like behaviour, which may be attributable to differences in genetic background or in variables such as housing conditions and diet between research groups (Dere et al., 2003; Dere et al., 2004; Acevedo, Ohtsu, Benice, Rizk-Jackson, & Raber, 2006; Acevedo, Pfankuch, Ohtsu, & Raber, 2006; Castellan Baldan et al., 2014). These mice do not perfectly capture the W317X point mutation in exon 9; rather, they contain an *Hdc* allele in which exons 6–9, in the middle of the gene, are replaced by a *Neo* cassette in reverse orientation. The effect of the two alleles is similar: They both produce truncated proteins with no ability to catalyse the conversion of histidine into histamine. We confirmed this, as histamine levels in several brain regions were undetectably low in KO mice and reduced by approximately 50% in heterozygotes.

In our initial analysis, these mice exhibited no evident tic-like repetitive behaviours at rest. However, when we administered a single dose of **D-amphetamine**, they exhibited markedly elevated stereotypy (primarily repetitive focused sniffing); this was mitigated by pretreatment with the dopamine D_2 receptor antagonist, **haloperidol**, which is an efficacious pharmacotherapy for tics (Castellan Baldan et al., 2014). Similarly, when exposed to acute behavioural stress, KO mice showed markedly elevated grooming, compared to sibling controls (Xu et al., 2015). Heterozygotes were intermediate in both cases. More recently, careful examination of exploratory activity in the open field at baseline has revealed an elevation in the complexity of repetitive behavioural sequences and of the frequency with which they are repeated in these mice. This abnormality was also mitigated by D_2 receptor antagonism (Santangelo et al., 2017). Thus, across several different behavioural paradigms, *Hdc* KO mice exhibit repetitive behavioural pathology, which (like tics) is responsive to acute stress, psychostimulant challenge, and D_2 receptor antagonists.

We also examined prepulse inhibition (PPI) in these mice. PPI is a well-established measure of sensorimotor gating; it is deficient in tic disorders and in several other neuropsychiatric conditions (Kohl, Heekeren, Klosterkotter, & Kuhn, 2013). Importantly, we were able to demonstrate impaired PPI in TS patients carrying the *Hdc* W317X allele, establishing that this specific form of TS (as opposed to tic disorders more generally) is characterized by abnormal sensorimotor gating. A similar effect was seen in *Hdc* KO mice; again, heterozygotes showed an intermediate deficit (Castellan Baldan et al., 2014). This parallelism between humans and mice provides important support for the validity of the model.

Several neurochemical observations in *Hdc* KO mice provide further parallelism to human TS. Both basal and amphetamine-induced markers of neuronal activity were elevated in the striatum in KO mice, as were basal dopamine levels (Castellan Baldan et al., 2014; Rapanelli et al., 2014). This parallels the dysregulated activity and dopamine tone that has been documented in the corticostriatal circuitry in TS (Pittenger, 2017b). Finally, the **dopamine D_3** receptor was elevated in the substantia nigra of *Hdc* KO animals; this likely represents a homeostatic response to chronic dopamine hyperstimulation. We were able to establish parallelism with TS patients: PET imaging of dopamine receptors in carriers of the *Hdc* W317X mutation revealed a similar elevation of $D_{2/3}$ receptors in the substantia nigra (Castellan Baldan et al., 2014). Again, parallel findings in human patients and the pathophysiological model increase confidence that the model is successfully reproducing disease-relevant processes.

There are a number of other genetically modified mice in which histamine signalling is perturbed, including histamine receptor KOs (Schneider et al., 2014a,b), and histamine deficits can also be produced pharmacologically (Santangelo et al., 2017). In light of the insight that histamine dysregulation can contribute to tic disorders, it may be interesting to probe tic-relevant phenotypes in these other systems. For example, PPI deficits have recently been described in H_3 receptor KO mice (Kononoff Vanhanen, Nuutinen, Tuominen, & Panula, 2016), and alterations in stereotyped behaviour patterns have been documented after pharmacological histamine depletion (Santangelo et al., 2017). However, it is important to recognize that not all disruptions of brain histamine signalling are likely to produce the same effects. *Hdc* KO mice are of particular value because they reproduce a mutation associated with disease, which these other manipulations do not (Castellan Baldan et al., 2014; Pittenger, 2017a).

The initial validation studies in the *Hdc* KO model set the stage for ongoing work, using the powerful methodologies and causal tests possible in mice, to ask new questions about pathophysiological mechanisms. Characterization of the KO mouse convincingly demonstrates that the *Hdc* null genotype is associated with tic-relevant behavioural and neurochemical abnormalities; but it leaves several key questions unanswered:

- Are these tic-relevant effects due to absence of histamine, or to some other, uncharacterized effect of the *Hdc* mutation?
- Are they due to reduced histamine in the adult, or to a more indirect or developmental process?
- Are these effects due to deficiency in neurotransmitter histamine derived from the hypothalamus, or a deficiency in peripheral sources of histamine?
- Are the causally relevant network effects localized to the dorsal striatum, where we characterized abnormalities in the initial study, or elsewhere in the brain?

These questions were addressed in a recent study in transgenic mice that nicely illustrates the power of causal analysis in model systems (Rapanelli, Frick, Bito, & Pittenger, 2017).

Hdc KO mice have dysregulation of both neuronal and peripheral histamine, throughout development. To isolate the effects of neurotransmitter histamine in the adult, we used a combination transgenic-viral strategy to engineer targeted ablation of histaminergic neurons in the posterior hypothalamus in developmentally normal mice. This resulted in pathologically elevated grooming—indeed, mice with targeted ablation of histaminergic neurons groomed so much that they removed large patches of hair from their faces, heads, and backs (Rapanelli, Frick, Bito, & Pittenger, 2017); this resembles the elevated grooming that has been described in several other animal models that purport to capture pathophysiology of various neuropsychiatric conditions (Kalueff et al., 2016). A similar effect was seen, albeit more transiently, when histaminergic neurons were chemogenetically inhibited. Elevated grooming was attenuated when histamine was infused into the dorsal striatum in conjunction with chemogenetic inactivation of the hypothalamus (Rapanelli, Frick, Bito, & Pittenger, 2017). This collection of experiments addresses all of the open questions listed above: It establishes that disruption of neurotransmitter histamine in an adult, independent of any developmental effects, is sufficient to produce repetitive behavioural pathology and that this effect depends on acute reduction of histamine in the dorsal striatum.

An additional series of experiments provides further evidence for the causal necessity and sufficiency of histamine effects in the dorsal striatum in this repetitive behavioural pathology. Transient histamine reduction, induced by chemogenetic inhibition of histaminergic neurons in the hypothalamus, led to elevated neuronal activity in the dorsal striatum. Using a novel multiplexed chemogenetic strategy, we labelled these activated neurons in the dorsal striatum, such that they could themselves be chemogenetically regulated at a later time point. Activation of these dorsal striatal neurons, without any simultaneous inhibition of the hypothalamus, was sufficient to produce elevated grooming, demonstrating sufficiency. Conversely, inhibition of these striatal neurons attenuated the grooming produced by inhibition of histaminergic neurons in the posterior hypothalamus, demonstrating necessity (Rapanelli, Frick, Bito, & Pittenger, 2017). Establishing necessity and sufficiency in this manner is not possible in patients and illustrates the power of probing pathophysiology in an animal model.

6 | DYSREGULATION OF THE HISTAMINE H_3 RECEPTOR IN THE *Hdc* KO MOUSE MODEL

Confirmation of the dorsal striatum as a locus of pathophysiology in the *Hdc* KO model, while hardly surprising, focuses attention on this structure for the identification of candidate molecular or cellular alterations. We systematically characterized expression of the four histamine receptors in the KO mice, at both the level of mRNA expression and of ligand binding ex vivo, and found the H_3 receptor to be markedly up-regulated (Frick, Rapanelli, Abbasi, Ohtsu, & Pittenger, 2016; Rapanelli, Frick, Pogorelov, et al., 2017; Figure 1a,b). This initially may seem irrelevant to understanding the mechanisms

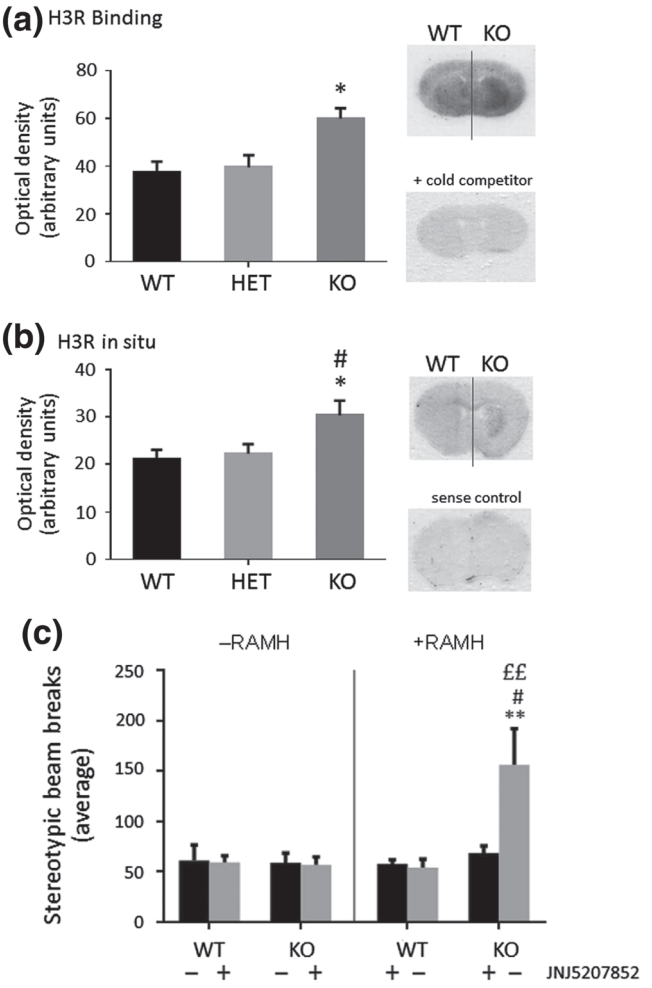

FIGURE 1 (a) Binding of a radiolabelled ligand for the H_3 receptor was increased in the striatum of *Hdc* KO mice. (b) mRNA for the H_3 receptor gene was similarly increased in the striatum of *Hdc* KO mice. In (a) and (b), $^{*}P < 0.05$, significantly different from WT; $^{\#}P < 0.05$, significantly different from heterozygotes (Het). (c) Stereotypic beam breaks in an open field apparatus, a form of repetitive behavioural pathology, were increased in *Hdc* KO mice after administration of the H_3 receptor agonist RAMH, compared to both WT mice administered RAMH and *Hdc* KO mice administered saline. This effect was blocked by coadministration of the H_3 receptor antagonist JNH5207852. $^{**}P < 0.01$, significantly different from WT-RAMH; $^{\#}P < 0.05$, significantly different from *Hdc*; $^{\pounds\pounds}P < 0.01$, significantly different from *Hdc* KO saline. All panels from Rapanelli, Frick, Pogorelov, et al. (2017)

underlying the abnormalities in the model: Why would it matter whether there are more histamine receptors if there is no histamine to bind them? But in the case of the H_3 receptor, there are at least two reasons to believe that the receptor may influence cell signalling and physiology, even though the KO mice have no histamine. The H_3 receptors have a high level of endogenous signalling through $G\alpha_i$, even in the absence of ligand (Morisset et al., 2000). Also, H_3 receptors can heterodimerize with D_1 and D_2 receptors (Ferrada et al., 2008; Ferrada et al., 2009; Moreno et al., 2011), as well as perhaps with the **σ receptor** (Moreno et al., 2014), and thus modulate signalling even in the absence of histamine.

The H_3 receptor appears to have several modes of signalling; these may differ in different neurons (Panula & Nuutinen, 2013). Classically, the H_3 receptor have been described as coupling to $G\alpha_i$ and to thereby reduce **cAMP** levels and has been characterized as a primarily presynaptic receptor, reducing release of both histamine itself (thus serving as a negative feedback mechanism) and of other neurotransmitters (Haas et al., 2008; Morisset et al., 2000; Schlicker, Malinowska, Kathmann, & Gothert, 1994). This mechanism has been confirmed electrophysiologically in the striatum, in which presynaptic H_3 receptors on glutamatergic afferents reduce **glutamate** release upon stimulation of excitatory cortical projections (Ellender et al., 2011). However, postsynaptic H_3 receptors also appear to be prominent in the striatum (Bolam & Ellender, 2015; Panula & Nuutinen, 2013). Postsynaptic H_3 receptors do not appear to signal primarily (if at all) through $G\alpha_i$. Rather, they heterodimerize with other receptors, including D_1 and D_2 receptors, and their signalling properties are regulated by this heterodimerization. In D_1 receptor-expressing medium spiny neurons (MSNs) of the striatum, for example, H_3 receptor activation triggers signalling pathways normally associated with D_1 receptor activation, including the **MAPK** pathway (Moreno et al., 2011; Moreno et al., 2014).

This regulation of signalling by heterodimerization implies that H_3 receptor expression and activation may have rather different effects on cellular signalling, and thus on electrophysiological properties and information processing, in different cell types. It also complicates the potential effects of pharmacological manipulations targeting the H_3 receptor. Whereas the simpler earlier model of H_3 receptors as a presynaptic inhibitory receptor predicted that H_3 receptor antagonists would disinhibit release of histamine (and other transmitters), the updated view predicts more complicated and varied responses.

Up-regulated H_3 receptors in the *Hdc* KO striatum (Rapanelli, Frick, Pogorelov, et al., 2017) are likely to be primarily postsynaptic, though this has not been demonstrated directly. We therefore set out to characterize H_3 receptor effects on signalling in the striatum, in vivo, and to examine them in the *Hdc* KO model system.

In wild type mice, H_3 receptor activation in vivo through systemic administration of an agonist such as **R-aminomethyl histamine** (RAMH) or **immepip** has complex effects (Rapanelli et al., 2016). Some effects reproduce what has been described ex vivo in studies of H_3–D_1 receptor heterodimers and are thus likely to be direct effects of the agonist on striatal neurons. Others are distinct and may represent indirect effects of H_3 receptor activation elsewhere in the circuitry. Such mechanistic details cannot be established with certainty in in vivo studies. On the other hand, examination of signalling in vivo allows direct correlation with systemic and behavioural effects.

There are two distinct populations of striatal MSNs, distinguished by their expression of different dopamine receptors: the D_1 receptor-expressing "direct pathway" MSNs, or dMSNs, and the D_2 receptor-expressing "indirect pathway" MSNs, or iMSNs. H_3 receptor signalling in these two populations is quite distinct, as predicted from the insight that signalling of postsynaptic H_3 receptors is determined by patterns of heterodimerization. It is therefore critical, though technically challenging, to examine signalling separately in these two cell populations. Interestingly, H_3 receptor agonist treatment does not detectably regulate cAMP signalling (measured by quantifying phosphorylation of the signalling regulator DARPP-32) in either MSN population, as would have been predicted from the canonical notion of $G\alpha_i$ coupling (Rapanelli et al., 2016).

In dMSNs, H_3 receptor activation leads to transient activation of signalling through the MAPK pathway and activation of the downstream target **rpS6**. This is similar to that seen after D_1 receptor activation, and what has been documented after H_3 receptor activation in ex vivo studies (Moreno et al., 2011). Treatment with H_3 receptor agonists also regulates signalling through the **Akt**/**GSK** pathway in dMSNs, leading to transiently increased phosphorylation (and thus presumed deactivation) of GSKβ at 15 min; the effect resolves by 45 min. This is not seen after activation of D_1 receptors, and the detailed mechanisms underlying this novel effect are not yet clear and require further study (Rapanelli et al., 2016). Interestingly, although activation of H_3 and D_1 receptors produces similar effects on MAPK signalling, they interfere with one another: Systemic coadministration of agonists of both receptors blocks MAPK activation (Rapanelli et al., 2016), as has been seen ex vivo (Moreno et al., 2011). Similarly, at the behavioural level, coadministration of the H_3 receptor agonists RAMH or immepip blocks the locomotor activation normally seen after administration of a D_1 receptor agonist (Rapanelli et al., 2016).

In D_2 receptor-expressing iMSNs, the pattern is quite different. Systemic RAMH administration produces no effects at all on MAPK but does regulate Akt/GSK. The direction of regulation, however, is the opposite of what is seen in D1R-expressing dMSNs, and the time course is different: Phosphorylation of GSKβ is decreased, with a trend at 15 min that becomes significant at 45 min (Rapanelli et al., 2016). The regulation of Akt/GSK signalling in iMSNs resembles the noncanonical β-arrestin-dependent signalling seen in these cells after activation of D_2 receptors (Beaulieu et al., 2005) and is thus consistent with the hypothesis that H_3–D_2 receptor heterodimerization (Ferrada et al., 2008) controls H_3 receptor signalling in these cells, although this hypothesis has yet to be directly tested. Functional interactions between D_2 and H_3 receptors have also been observed at the behavioural level (Ferrada et al., 2008; J. Xu and C. Pittenger, 2018, unpublished observations), though the effect is not as robust or as clearly documented as in the case of D_1–H_3 receptor functional interactions.

As a first test of the functional significance of H_3 receptor overexpression in the *Hdc* KO model, we administered the H_3 receptor agonist RAMH to KO and wild type animals, reasoning that agonist treatment should further accentuate any effects of the over-expressed H_3 receptor. It was not obvious, a priori, what the effect of such an accentuation would be. As H_3 receptor signalling can antagonize D_1 receptor effects ex vivo and in vivo (Moreno et al., 2011; Rapanelli et al., 2016), one might predict that H_3 receptor up-regulation would serve as a compensation for dopaminergic excess and thus that further activation of H_3 receptor signalling might attenuate repetitive behavioural pathology in the *Hdc* KO model. Such a result would suggest that H_3 receptor up-regulation in the KO mice is a compensation. Alternatively, as H_3 receptor activation in the absence of dopamine can activate MAPK signalling in dMSNs, it might be expected to exacerbate pathology. Our data support the latter of these two possibilities.

In wild types, RAMH produced no strong behavioural effect, even at high doses. In KOs, on the other hand, RAMH challenge produced repetitive behaviours (Rapanelli, Frick, Pogorelov, et al., 2017; Figure 1c). Using a chemogenetic strategy, identical to that described above in our studies of the effects of hypothalamic silencing (Rapanelli, Frick, Bito, & Pittenger, 2017), we demonstrated that here, too, increased activation of cells in the dorsal striatum was both necessary and sufficient for the repetitive behavioural pathology (Rapanelli, Frick, Pogorelov, et al., 2017). The specific form of repetitive behaviours—stereotypic beam-breaking in an open field—was distinct from both the focused sniffing stereotypy seen after amphetamine (Castellan Baldan et al., 2014) and the increased grooming seen after acute stress (Xu et al., 2015). This emphasizes that the precise nature of the repetitive behavioural pathology seen in a particular experiment may depend on experimental details, rather than on fundamental characteristics of the model, reinforcing the importance of remaining agnostic as to the details of what a "tic-like" behaviour should look like in an animal model system. But the fact that repetitive behavioural pathology, of one form or another, is seen in the *Hdc* KO model after three quite distinct perturbations reinforces the conclusion that the corticobasal ganglia circuitry is destabilized in these animals.

Previous work established dysregulation of both MAPK and Akt signalling pathways in the dorsal striatum of *Hdc* KO mice, both at baseline and after amphetamine challenge (Rapanelli et al., 2014). More recently, we have examined differential dysregulation of these signalling pathways in D_1- and D_2 receptor-expressing MSNs (Rapanelli et al., 2018). Strikingly, we find abnormalities at baseline in the KO mice that are nearly identical to what is seen in wild type animals after systemic administration of a H_3 receptor agonist. In D_1 receptor-expressing dMSNs, activation of the MAPK signalling pathway is elevated. In D_2 receptor-expressing iMSNs, MAPK activity is normal, but phosphorylation of Akt is reduced (Rapanelli et al., 2018). This parallelism—that signalling at baseline in the KOs so closely reproduces what is seen after H_3 receptor agonist treatment in wild types—is consistent with the proposal that constitutive effects of up-regulated H_3 receptors in the striatum of *Hdc* KO mice explain much of the striatal dysregulation seen in these animals. Direct testing of this hypothesis is underway.

7 | IMPLICATIONS AND FUTURE DIRECTIONS

If up-regulation of the H_3 receptor can destabilize the corticostriatal circuitry and contribute to tic pathophysiology, as suggested above, then it emerges as a potential focus of pathophysiological insight and a target for novel treatments.

While H_3 receptors can be visualized using PET (Funke et al., 2013), no studies to date have done so in individuals with tics. The H_3 receptor gene (*Hrh3*) did not emerge as differentially expressed in the brain of individuals with TS in the one post-mortem transcriptomic study that has been described to date (Lennington et al., 2016). On the other hand, histaminergic genes, including *Hrh3*, have been reported to be altered in the striatum of individuals with autism (Wright et al., 2017), suggesting a possible association with a broader neuropsychiatric phenotype. More work of this sort is needed to clarify what diagnoses or symptoms H_3 receptor dysregulation might be most closely associated with in humans.

A single case report of an individual with tics and narcolepsy who was treated with the H_3 receptor antagonist/inverse agonist **pitolisant** has been published, in which there was benefit to scores of daytime sleepiness but no reduction in tic severity (Hartmann, Worbe, & Arnulf, 2012). An unpublished controlled study of an H_3 receptor antagonist/inverse agonist in adolescents with TS has been described (www.clinicaltrials.gov: NCT01904773), using the drug AZD5213 (Jucaite et al., 2013). The design involved multiple crossovers between placebo and two doses of drug. Unexpectedly, when subjects were treated with the higher dose of drug, they exhibited a small but statistically significant worsening of tic symptoms, compared to placebo (P = 0.0087). Tics after treatment with the lower dose of drug were intermediate, though they did not differ statistically from placebo (www.clinicaltrials.gov: NCT01904773).

This worsening of tics is obviously a disappointing result, from the perspective of drug development, but it may be interpreted as confirming the relevance of the receptor to pathophysiology. The finding must be interpreted with caution, as this was a small study with a complex design, and the time of drug exposure was relatively brief (4 weeks). Provisionally accepting the result, however, raises the possibility that both a H_3 receptor antagonist, in the clinical study (NCT01904773), and a H_3 receptor agonist, in our investigation in the KO model (Rapanelli, Frick, Pogorelov, et al., 2017), can exacerbate repetitive behavioural pathology. This surprising result may derive from the complex distribution and multiple roles of the H_3 receptor. Specifically (for example), a H_3 receptor antagonist acting heterosynaptically on axon terminals might worsen symptoms by increasing dopamine tone (Schlicker et al., 1994) or disinhibiting corticostriatal afferents (Ellender et al., 2011), while an agonist acting on postsynaptic H_3 receptor heterodimers could disinhibit striatal MSNs (Rapanelli, Frick, Pogorelov, et al., 2017). These mechanistic speculations, which require

more detailed investigation and empirical refinement, raise the possibility that therapeutic benefit from targeting the H_3 receptor in tic disorders may require the development of new agents that select for this receptor in specific contexts or on specific cells—for example, antagonists that bind to specific postsynaptic heterodimer complexes but not to the presynaptic receptors.

In spite of these specific questions about pharmacological development, the series of studies reviewed above highlights the potential power of new advances in the genetics of complex neuropsychiatric disease and of mechanistic analysis of models of pathophysiology derived from these new insights. It is to be hoped that ongoing work in the *Hdc* KO model, and in other models that may be developed from further accruing genetic findings (Willsey et al., 2017), will pave the way to new and generalizable insights into pathophysiology and ultimately to new strategies for disease treatment and prevention.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander, Fabbro et al., 2017; Alexander, Christopoulos et al., 2017).

ACKNOWLEDGEMENT

This work was supported by National Institute of Mental Health Grant R21MH109700.

CONFLICT OF INTEREST

C.P. reports no competing interests of relevance to this work; he is a consultant to Biohaven Pharmaceutical Holding Corporation and is performing contracted research for Biohaven Pharmaceutical Holding Company and Blackthorn Therapeutics, Ltd. on other topics and receives royalties from Oxford University Press.

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How to cite this article: Pittenger C. The histidine decarboxylase model of tic pathophysiology: a new focus on the histamine H_3 receptor. *Br J Pharmacol*. 2020;177:570–579. https://doi.org/10.1111/bph.14606