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Histidine decarboxylase knockout mice as a model of the pathophysiology of Tourette syndrome and related conditions

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Abstract

While the normal functions of histamine (HA) in the central nervous system have gradually come into focus over the past 30 years, the relation of abnormalities in neurotransmitter HA to human disease has been slower to emerge. New insight came with the 2010 description of a rare nonsense mutation in the biosynthetic enzyme histidine decarboxylase (*Hdc*) that was associated with Tourette syndrome (TS) and related conditions in a single family pedigree. Subsequent genetic work has provided further support for abnormalities of HA signaling in sporadic TS. As a result of this genetic work, *Hdc* knockout mice, which were generated more than 15 years ago, have been reexamined as a model of the pathophysiology of TS and related conditions. Parallel work in these KO mice and in human carriers of the *Hdc* mutation has revealed abnormalities in the basal ganglia system and its modulation by dopamine (DA) and has confirmed the etiologic, face, and predictive validity of the model. The *Hdc*-KO model thus serves as a unique platform to probe the pathophysiology of TS and related conditions, and to generate of specific hypotheses for subsequent testing in humans. This chapter summarizes the development and validation of this model and summarize recent and ongoing work using it to further investigate pathophysiological changes that may contribute to TS and related conditions.

Keywords

histamine; *histidine decarboxylase*; Tourette syndrome; tic disorders; obsessive-compulsive disorder; animal model

INTRODUCTION

Histamine (HA) is a biogenic amine that has long been appreciated to have important roles in the periphery, particularly in the regulation of inflammation (Falus et al., 2004). It was recognized as a neurotransmitter in 1984, when Panula and colleagues identified HA-positive neurons in the posterior hypothalamus (Panula et al., 1984). Since that time, a substantial literature has examined the functions of neurotransmitter HA throughout the brain (Haas et al., 2008; Panula and Nuutinen, 2013).

A new window into the role of histamine dysregulation in neuropsychiatric disease was opened by a landmark 2010 genetic study. A combination of linkage analysis and exome sequencing in a family with an exceptionally high incidence of Tourette syndrome (TS),

together with a range of comorbid conditions, identified a rare nonsense mutation in the gene *histidine decarboxylase* (*Hdc*) that segregated with the TS phenotype (Ercan-Sencicek et al., 2010). *Hdc* encodes the enzyme that converts the amino acid histidine into HA and is essential for HA biosynthesis in mammals (Haas et al., 2008). This genetic finding represented the first time that HA dysregulation had been associated with TS.

The TS-associated *Hdc* mutation has a number of characteristics that make it particularly well suited for study in animals, as further elaborated below. *Hdc* knockout mice were generated 15 years ago by Ohtsu and colleagues (Ohtsu et al., 2001) and had been studied in a variety of contexts, but they had not been conceived as a model of TS prior to 2010. Since then, a number of studies have examined these mice a potential model of the pathophysiology of TS. Studies to date have established the validity of the model at several levels (Castellan Baldan et al., 2014), motivating ongoing work to use these animals as a platform for further investigations of the pathophysiology of TS and related disorders. This work is summarized in this chapter.

Clinical features and pathophysiology of tic disorders

Tics are sudden, rapid, recurrent, non-rhythmic, semi-voluntary movements. Simple tics include such movements as blinking, sniffing, grunting, and turning the head; they are most common in the face but can affect any part of the body. Tics can also be more complex and can incorporate multi-step head, arm, or trunk movements and more complex utterances, including complete words or phrases. The spasmodic production of profanity, or coprolalia, is rare, but represents a particularly striking form of complex vocal tic. Tics are described as semi-voluntary, because most individuals (especially adults) are aware of a sense of tension or discomfort preceding the tic; this is known as a ‘premonitory urge’. A tic discharges this tension, much as a sneeze discharges a growing discomfort in the back of the nose. Most individuals with tics can suppress them to an extent; however, as with a sneeze, suppressing a tic requires effort and is typically accompanied by increasing discomfort. Tics are lessened by relaxation, sleep, and focused concentration; they are worsened by stress and sleep deprivation (Du et al., 2010; Leckman, 2002).

Tics are common, occurring in mild forms in approximately 20% of young people; clinically significant tics occur in about 5%. Tourette syndrome consists of chronic motor and vocal tics, beginning in childhood and persisting for at least a year; it affects ~1% of the population (Robertson et al., 2009; Scahill et al., 2001). Tics and TS are more common in males, with a sex ratio of ~3:1 (Scahill et al., 2001; Scharf et al., 2012). They are also more common in children; approximately 75% of children with a clinically significant tic disorder will improve to the point that they no longer have clinically significant tics by young adulthood (Leckman, 2002).

‘Pure’ TS is uncommon: up to 90% of individuals with a diagnosis of TS carry at least one additional diagnosis, most commonly obsessive-compulsive disorder (OCD) and attention deficit-hyperactivity disorder (ADHD) (Hirschtritt et al., 2015). Tics are also commonly seen in individuals with autism spectrum disorder (ASD) (Canitano and Vivanti, 2007). Given this high level of comorbidity, the pathophysiology of tics can be expected to overlap with that of some of these other conditions. A relationship with OCD is particularly clear

and has been the subject of considerable study (Pittenger, 2017). TS and OCD often run together in families and have some shared genetic risk (Davis et al., 2013; Du et al., 2010). Both are associated with dysregulation of the cortico-basal ganglia circuitry (Leckman et al., 2010; Maia et al., 2008).

Current understanding of the neurobiology of TS is limited. Structural neuroimaging studies have implicated the striatum and afferent cortical areas: the caudate and putamen are slightly but significantly smaller in both children and adults with TS, and afferent sensorimotor cortical areas are thinner (Leckman et al., 2010; Pittenger, 2017). Functional neuroimaging suggests phasic abnormalities in activity in this circuitry; tics are associated with increased activity in motor and premotor areas and in the putamen, while effortful tic suppression is associated with activity in more anterior frontal areas and in the caudate. The supplementary area (SMA) is particularly clearly implicated in TS: activity in the SMA uniquely differentiates tics from topographically similar volitional movements (Hampson et al., 2009); and stimulation of the SMA in humans produces both tic-like movements and accompanying urges (Fried et al., 1991).

Several pathophysiological theories of TS, which are by and large not mutually exclusive with one another, have been advanced (Pittenger, 2017). One proposal is that TS is associated with elevated dopamine (DA) tone in the striatum. This proposal is based on several observations. First, dopamine D_2R receptor blockers are the most efficacious pharmacotherapy for tics (though their use is limited by their side effects) (Bloch, 2008). Second, psychostimulant drugs and DA agonists can trigger stereotypic behaviors in rodents that have been interpreted as tic-like (Canales and Graybiel, 2000); supratherapeutic psychostimulant challenge can trigger or transiently worsen tics in patients (Denys et al., 2013; Feinberg and Carroll, 1979). Third, some neurochemical imaging studies, though not all, suggest elevated basal and evoked dopamine release in the striatum in patients with tics (Denys et al., 2013; Singer et al., 1992; Wong et al., 2008).

The striatum is the largest nucleus of the basal ganglia and their primary input; in primates, it consists of the caudate and putamen, though these are not discrete structures in rodents. Projections to the striatum and thence to the deeper components of the basal ganglia have classically been described as consisting of two parallel systems, termed the direct and indirect pathway. This scheme is a simplification but is of considerable heuristic value; it appears to be particularly applicable in the dorsal striatum (Figure 1). Striatal medium spiny neurons (MSNs) of the direct pathway (dMSNs) express D_1R dopamine receptors and have a polysynaptic disinhibitory effect on the thalamic output of the basal ganglia system. MSNs of the indirect pathway (iMSNs) express D_2R dopamine receptors and polysynaptically inhibit the thalamus. Recent data support the idea that these two pathways work in synergy in the process of action selection, with the direct pathway promoting a selected action through disinhibition of relevant thalamocortical feedback, while the indirect pathway inhibits off-target actions through thalamic inhibition (Cui et al., 2013; Hikosaka et al., 2000; Mink, 2003). In TS, a modest elevation of tonic DA is likely to primarily affect D_2R receptors on MSNs of the indirect pathway, because the D_2R receptor has a much higher affinity for DA than the D_1R receptor. The D_2R receptor reduces firing of MSNs of the indirect pathway, and so increased D_2R tone is predicted to lead to disinhibition of off-target

behaviors – which may, it has been proposed, manifest as tics (Albin et al., 1989; Mink, 2001, 2003; Pittenger, 2017).

A related model is that TS is associated with abnormal inhibition in the striatum. More specifically, localized foci of disinhibition have been proposed to produce domains of autonomous neuronal firing, which manifest as tics (Albin and Mink, 2006). This has been directly tested in animals: injection of GABA-A receptor antagonists into the monkey striatum produce tic-like movements of the contralateral limb and face (Bronfeld and Bar-Gad, 2013; McCairn et al., 2009). Similar phenomena have been documented in rats and mice (Bronfeld et al., 2013; Pogorelov et al., 2015). Post-mortem studies of individuals with severe, refractory tics have documented interneuronal abnormalities in the striatum, providing a potential explanation for deficient inhibition (Kalanithi et al., 2005; Kataoka et al., 2010; Lennington et al., 2016). And targeted disruption of inhibitory interneurons in otherwise normal mice enhances repetitive movements, providing support for a causal role for disrupted intrastriatal inhibition in the development of tics (Xu et al., 2015a; Xu et al., 2016).

A final perspective on the pathophysiology of TS, OCD, and related conditions, somewhat less well specified than the preceding, focuses on the dysregulation of neuroinflammatory processes. This focus derives from the observation that individuals with TS often exhibit other evidence of dysregulated immune function (Elamin et al., 2013). An extreme example of this is seen in the syndrome of pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus*, in which an autoimmune reaction triggered in a susceptible host by a Streptococcal infection is thought to lead to basal ganglia inflammation (Williams and Swedo, 2015). But activation of microglia, the brain's principle inflammatory cells, has also been seen in TS more generally, both *in vivo* (as measured by PET imaging using a marker of microglial activation (Kumar et al., 2015)) and *post mortem* (Lennington et al., 2016). Furthermore, individuals with TS, as a group, exhibit abnormalities in a number of peripheral immunological markers (Elamin et al., 2013). Several animal models have demonstrated that experimentally induced microglial abnormalities can produce repetitive behavior, typically elevated grooming (Chen et al., 2010; Zhan et al., 2014). Thus, while the details remain to be established, microglial activation and dysregulated neuroimmune interactions are an increasing focus of interest in the study of TS pathophysiology (Frick and Pittenger, 2017).

These various pathophysiological considerations allow us to enumerate a number of testable predictions that can be investigated in any model of TS. In addition to behavioral phenotypes (repetitive movements; prepulse inhibition deficits), a valid model of TS may be expected to exhibit modest elevations in tonic striatal DA, tonic or phasic alterations in striatal neuronal activity, abnormalities in striatal inhibition, and possibly abnormalities in neuroinflammatory processes.

Animal models of tic disorders

A number of studies over the past 30 years have sought to model tic pathophysiology in animal models (Godar et al., 2014; Pittenger, 2014). Analysis of the *Hdc*-knockout model, described in more detail below, has drawn on approaches and principles established in this

previous work, which motivates discussion of past models here. It is important to acknowledge at the outset that no animal model of TS (or of OCD, or of any other complex neuropsychiatric condition) should be expected to recapitulate the human syndrome in its entirety (Pittenger, 2014; Pittenger et al., 2017).

There are several reasons for this. First, human neuropsychiatric syndromes are themselves complex and heterogeneous categories that may not represent natural kinds and are likely to be recharacterized and recategorized as understanding of pathophysiology advances (Insel and Cuthbert, 2015). Second, important aspects of TS are not readily assessed in an animal: for example, repetitive, tic-like behaviors can be observed and quantified, but it is impossible to assess whether they are associated with the premonitory urges that are characteristic of tics. Conversely, it may be unclear what human symptom (if any) a repetitive behavior in an animal best recapitulates: a repetitive behavior such as elevated grooming (Kalueff et al., 2016) could be homologous to tics, but it could as easily be argued to recapitulate symptoms of autism (Peca et al., 2011), OCD (Greer and Capecchi, 2002; Shmelkov et al., 2010; Welch et al., 2007), trichotillomania (Feusner et al., 2009), or some other condition. It is thus perilous to interpret the disease-relevance of an animal model or of a particular behavioral phenotype based solely on its resemblance to human symptomatology (that is, on its face validity) (Pittenger et al., 2017).

Finally, while the overall anatomical organization of the cortico-basal ganglia system is preserved between humans and rodents, there are key differences, such as the prominence of the globus pallidus interna (equivalent to the entopeduncular nucleus, which is fairly rudimentary, in rodents), and the fraction of basal ganglia output that projects to thalamus (predominant in humans) versus midbrain and brainstem structures (predominant in rodents). Because of these differences, even a rodent model that captures core pathophysiology perfectly might have behavioral consequences that are not perfectly isomorphic to tics.

For these reasons, it is better to speak of models that capture aspects of the pathophysiology of a disorder, rather than a disorder in its entirety. Such models are at their strongest when they are based on a clear causal hypothesis – that is, when they have clearly specified construct or etiologic validity (Pittenger et al., 2017). A series of such models have been described in TS and are contributing to increased understanding of the disorder (Godar et al., 2014; Pittenger, 2014, 2017). The most informative models can be understood as testing specific hypotheses of the pathophysiology of TS.

As noted above, pharmacological treatments that increased dopamine or dopamine receptor tone, such as psychostimulants, produce repetitive stereotypic behaviors that have some characteristics of tics (Iversen and Creese, 1975; Lyon and Robbins, 1975). This phenomenon provided early support for the idea that elevated dopamine levels may explain, or at least contribute to, the development of tics. These stereotypic movements after psychostimulant treatment have been observed to correlate with preferential activation of striosomes, neurochemically and synaptically distinct patches of cells within the striatum (Canales and Graybiel, 2000). Whether tics correspond to differential activity in striosomes

in humans is difficult to test and has not been clearly established, and the validity of amphetamine-induced stereotypies as a model of tics has been questioned (Pittenger, 2014).

As noted above, neuroimaging data suggest that corticostriatal circuits are dysregulated and hyperactive in both TS and OCD (Leckman et al., 2010; Maia et al., 2008). Experimental activation of these circuits constitutes a test of the hypothesis that such dysregulation can lead to repetitive, tic-like behaviors. This was first done in a transgenic model described by Burton and colleagues almost 20 years ago (Campbell et al., 1999; Nordstrom and Burton, 2002). They expressed a transgene that increases neural activity – the alpha subunit of the cholera toxin – in a subset of D_1R -expressing neurons in the forebrain. This leads to hyperactivity of both cortical and amygdalar projections to the striatum, and corresponding behavioral perseveration, grooming abnormalities, repetitive jumping, and other abnormalities. More recently, a more precise optogenetic approach has been used to perturb cortical projections to the striatum (from the orbitofrontal cortex, in this case); brief daily stimulation of striatal afferents has been found to result in persistently elevated repetitive behaviors (grooming) (Ahmari et al., 2013). In neither of these cases are the repetitive behaviors wholly isomorphic to tics; but the ability of experimentally induced dysregulation of the corticostriatal circuitry can produce repetitive behaviors supports the association of abnormal cortico-striatal activity with TS-relevant phenomenology.

Animal model evidence that disrupted local inhibition within the striatum can produce tic-like repetitive behavioral pathology (Bronfeld et al., 2013; McCairn et al., 2009; Pogorelov et al., 2015) or elevated grooming (Xu et al., 2015b; Xu et al., 2016) is reviewed above. These studies confirm the ability of inhibitory deficits within the basal ganglia circuitry to produce TS-relevant effects.

Genetics of TS: a focus on rare genes of large effect

TS is substantially genetic; recent estimates place heritability at approximately 50% (Davis et al., 2013). However, specific genetic risk factors have been slow to emerge (Fernandez et al., 2017). The one genome-wide association study (GWAS) reported to date identified a few suggestive associations, but none that reached the statistical threshold of genome-wide significance (Scharf et al., 2013).

Common risk alleles of small effect size will no doubt emerge from GWAS analyses as more subjects are studied. However, such mutations are of limited value in the modeling of pathophysiology in animals: recapitulation in an animal of a mutation that increases the risk of developing TS only modestly is likely to have very subtle effects. For a mutation to recapitulate pathophysiology in an animal model, it should ideally have a large effect size, such that carriers are extremely likely to develop disease (i.e., the mutation can be described as a cause of disease, not just a risk factor). Such mutations are invariably rare, and thus difficult or impossible to identify using GWAS methods. Despite their rarity and the attendant challenges of discovering and characterizing them, investigation of such rare mutations of large effect has proven to be of substantial value in other contexts (Geschwind and State, 2015).

In TS, several genes have been identified in which rare mutations of large effect are potentially causative (Fernandez et al., 2017). The first to be described, *Slitrk1*, was identified in a patient in which the gene was disrupted by a chromosomal translocation. Subsequent work identified a nonsense mutation and a mutation disrupting a 3' regulatory site on the mRNA, both of which were associated with TS (Abelson et al., 2005). The functions of *Slitrk1* are not well understood, but it is expressed at high levels in the developing brain (Stillman et al., 2009) and can regulate dendritic outgrowth (Abelson et al., 2005). Despite the genetic evidence that mutations in this gene can cause TS, knockout mice have mood and anxiety phenotype, and have not been reported to exhibit abnormal movements (Katayama et al., 2010). This animal model has yet to shed light on TS pathophysiology.

In contrast, a second rare mutation associated with TS, in the gene *Hdc*, has produced a highly informative animal model. This is the focus of the remainder of this chapter.

Histidine decarboxylase mutations and other disruptions of HA neurotransmission in TS

In 2010, State and colleagues described a two-generation pedigree in which a father and eight children all had chronic tics or TS (Ercan-Sencicek et al., 2010). The mother and her extended family had no history of TS, OCD, or related diagnoses. Linkage analysis in this pedigree identified a single interval, on chromosome 15, that segregated with the TS phenotype. Exome sequencing of this interval identified a single coding-frame mutation: a nonsense mutation, W317X, in *histidine decarboxylase*. This mutation truncates the protein and renders it catalytically inert – in fact, *in vitro* evidence suggests that the truncated protein functions as a dominant negative, inhibiting the ability of wild-type protein to catalyze the conversion of histidine into histamine (Ercan-Sencicek et al., 2010).

This study focused attention on the potential role of HA dysregulation in the development of TS for the first time (Bloch et al., 2011). However, the *Hdc* W317X mutation is vanishingly rare. Two subsequent genetic studies support the possibility that HA dysregulation contributes to TS more broadly (though still, most likely, in a minority of cases). First, Fernandez and colleagues performed a copy number variation (CNV) analysis in individuals with TS (Fernandez et al., 2012). While *Hdc* itself was not disrupted by any of the detected CNVs, unsupervised pathway analysis of genes affected by CNVs in TS implicated disruption of HA-mediated signaling. Second, Karagiannidis and colleagues examined markers of common variants at the *Hdc* locus in several hundred individuals with TS, and matched controls, and found overtransmission of a particular haplotype in patients; this suggests a contribution of common variants at this locus to disease risk (Karagiannidis et al., 2013). HA dysregulation is almost certainly still a rare cause of TS, but these findings suggest that it is not unique to the originally described *Hdc*-W317X family (Ercan-Sencicek et al., 2010).

To be harnessed for studying pathophysiology in an animal model, a disease-associated mutation should ideally have several characteristics; the *Hdc*-W317X mutation has all of them, and is thus particularly well suited for reverse translational analysis. First, as noted above, a disease-associated mutation is most likely to yield insights into pathophysiology if it has a large effect on disease risk. In the case of the *Hdc*-W317X mutation, every carrier

who has been characterized to date (all in the originally described family) has TS or chronic tics, suggesting a large effect. Second, the mutation ideally has a known, quantifiable effect on a gene of known function. This is true in the case of *Hdc*-W317X: the function of the encoded enzyme is known (it is critical for the biosynthesis of HA), and the effect of the mutation is well established and quantifiable (it completely abrogates HA biosynthesis). Finally, a disease-associated mutation is more convincing if it implicates systems with a plausible link to established pathophysiology. While a link between HA neurotransmission and TS was not contemplated until a few years ago, the link is *a priori* plausible: as reviewed elsewhere (Haas et al., 2008; Panula and Nuutinen, 2013), including in other chapters in this volume, neurotransmitter HA modulates DA (Castellan Baldan et al., 2014; Schlicker et al., 1994) and basal ganglia function (Bolam and Ellender, 2015), both of which are implicated in TS.

The *histidine decarboxylase* knockout mouse as a model of TS pathophysiology: Initial validation

These considerations have motivated examination of mice in which the *Hdc* gene is mutated as a potential model of the pathophysiology of TS (Table 1). Initial work has not recapitulated the W317X mutation but rather has examined mice in which the *Hdc* gene is inactivated using conventional knockout technology; these mice were first described 15 years ago (Ohtsu et al., 2001). *Hdc* full knockout mice are unable to synthesize HA; while some studies have suggested low persistent levels of HA (Ohtsu et al., 2001), in these studies, HA levels in the brain are so low as to be undetectable (Castellan Baldan et al., 2014). Heterozygotes have intermediate levels of HA in brain (Castellan Baldan et al., 2014), which is important: while it has not been possible to directly assay HA levels in brain in human carriers of the *Hdc* W317X mutation, they are presumably reduced, but not zero. Therefore, while *Hdc* full knockout mice are useful probes of pathophysiology, heterozygotes may be closer to the human disease state; they have been included in some, but not all, of the analyses discussed here. This consideration also reduces the importance of any potential residual HA in the brains of KO mice: the presence of low levels of HA, below what the level of detection, does not undermine the utility of these animals as a tool to probe processes of potential relevance to TS pathophysiology.

As noted, *Hdc* knockout mice were generated years ago, and they have been characterized in a range of behavioral and neurochemical experiments, by a number of different authors (Schneider et al., 2014); they have also been extensively characterized in assays of inflammatory and immune processes (Ohtsu, 2010). Some findings may be interpreted, in retrospect, as being of relevance to the pathophysiology of TS. For example, *Hdc*-KO mice have been reported to have increased DA turnover in the striatum, suggestive of altered dopaminergic modulation (Dere et al., 2003). Other studies have examined anxiety-like, depression-like, learning, and other phenotypes, with variable results (Acevedo et al., 2006a; Acevedo et al., 2006b; Dere et al., 2004; Schneider et al., 2014).

At baseline, no tic-like movements, elevated grooming, or any other repetitive behavior of potential relevance to TS were evident in *Hdc*-KO mice. Exploratory behavior in an open field, rearing, anxiety-like behavior (Castellan Baldan et al., 2014), and fear conditioning

(Xu et al., 2015b) were normal. This normal baseline behavior is at odds with some previous reports (Acevedo et al., 2006a; Dere et al., 2004). One possible explanation for this discrepancy is that different investigators have examined these mice on different genetic backgrounds (Schneider et al., 2014). These studies have been performed in males, extensively backcrossed (>N9) onto C57Bl/6. Regardless, normal baseline exploratory behaviors in these animals simplify interpretation of other behavioral phenotypes in these experiments.

Tics in TS fluctuate dramatically (Leckman, 2002); they are potentiated by such factors as acute stress (Buse et al., 2014; Conelea and Woods, 2008), sleep deprivation, and supratherapeutic doses of psychostimulants (Denys et al., 2013; Feinberg and Carroll, 1979). To further investigate tic-like phenomenology in the *Hdc*-KO mice, therefore, mice were acute challenged with a high dose of the psychostimulant D-amphetamine. At a dose that produces locomotor activation but few stereotypies in a wild-type mouse (on this genetic background), stereotypies were markedly enhanced in the KO animals. At a slightly higher dose, many of the KO animals became completely immobile; heterozygotes had elevated stereotypies (Castellan Baldan et al., 2014). Pretreatment with the D_2R antagonist haloperidol, which is an efficacious treatment for tics (Bloch, 2008), mitigated these stereotypies, endowing the model with a degree of predictive validity (Castellan Baldan et al., 2014) (Figure 2A). A similar interactive effect was seen after acute stress, induced by cued fear conditioning: KO animals showed elevated repetitive behavior (grooming, in this case) after the induction of stress, but not at baseline (Xu et al., 2015b) (Figure 2B).

The face validity of these two repetitive behavioral phenotypes is open to question; certainly neither the repetitive stereotypic sniffing seen after amphetamine challenge nor the elevated grooming seen after stress are as clearly isomorphic to tics as the unilateral, spasmodic, non-rhythmic movements seen after focal striatal inhibition in other models (Bronfeld and Bar-Gad, 2013; Bronfeld et al., 2013; McCairn et al., 2009; Pogorelov et al., 2015). However, face validity is a fickle guide in the interpretation of animal models of tic pathophysiology (Pittenger, 2014); indeed, as argued above, both the complexity of neuropsychiatric phenotypes and the differences between human and rodent neuroanatomy suggest that even optimal recapitulation of tic pathophysiology in a mouse might produce behavioral effects that do not look identical to human tics. Therefore, in these experiments, and in other TS models (Xu et al., 2015b; Xu et al., 2016), a range of repetitive behaviors are accepted as tentatively confirmatory of relevance to TS. The claim to relevance to tics derives not from the specific topography of the behavior, but rather from the recapitulation of underlying pathophysiological processes – in this case, disruption of the *Hdc* gene. Put another way: an elevated grooming phenotype in isolation is difficult to interpret with respect to any particular neuropsychiatric diagnosis (Kalueff et al., 2016) and is unavoidably ambiguous; but an elevated grooming phenotype in conjunction with a clear recapitulation of a hypothesized causal factor, like *Hdc* gene disruption (Xu et al., 2015b), may be interpreted, at least provisionally, as confirmatory of the underlying causal hypothesis.

While tics are central to the diagnosis of TS, patients with tics typically have a range of other abnormalities, some of which are described above. Some, like the presence of premonitory urges before tics and the ability to effortfully suppress them, are difficult to

assess in an animal model; but others can be assayed across species. A deficit in sensorimotor gating, indexed by prepulse inhibition (PPI), is in the latter category. Individuals with TS have deficient PPI (Castellanos et al., 1996; Kohl et al., 2013; Swerdlow et al., 2001), as do individuals with OCD (Ahmari et al., 2012; Hoenig et al., 2005; Kohl et al., 2013). PPI was tested both in human carriers of the *Hdc*-W317X mutation and in *Hdc*-KO mice. PPI of the acoustic startle reflex was impaired in both, compared to normal controls. In the mice, baseline startle was increased by *Hdc* knockout, but the deficit in PPI persisted after controlling for this effect. Importantly, heterozygotes – which, as noted above, may better recapitulate partial HA deficiency in the patients than do the KOs – showed an intermediate PPI deficit (Castellan Baldan et al., 2014). These PPI findings provide an additional behavioral parallel between TS patients and the *Hdc*-KO model (Figure 2C).

Pathophysiological mechanisms in the *Hdc*-KO model: Dopamine and dopamine receptors

With this validation in hand, candidate pathophysiological processes in the *Hdc*-KO model were investigated. The initial focus was on dopamine modulation of the striatum; as reviewed above, convergent evidence suggests a modest elevation in tonic striatal DA in patients with tics (Pittenger, 2017). Similar effects were predicted in the model.

Direct measurement of tonic extrasynaptic DA levels is possible using *in vivo* microdialysis. In the knockout animals, baseline striatal DA was elvated (Rapanelli et al., 2014). This baseline elevation was accentuated in the animals' dark phase, when HA is normally elevated in mice (which are nocturnal); HA is of course absent in the KO animals, and thus this enhanced DA elevation in the dark cycle is consistent with negative regulation of DA by HA (Castellan Baldan et al., 2014). To directly test this, the effects of infusion of HA on DA levels were measured *in vivo* using microdialysis, in wild-type mice. As predicted, intacerebroventricular HA infusion reduced striatal DA levels (Castellan Baldan et al., 2014). This elevation in tonic extrasynaptic DA, which accords with current thinking about TS, provides further confirmation that the *Hdc*-KO model is recapitulating key aspects of pathophysiology.

What is the mechanism of this reduction in striatal DA levels by HA, and of the elevation in DA seen in the KO animals? Histamine binds to four G-protein-coupled receptors, H_1R-H_4R; H_1R-H_3R are expressed on neurons in the central nervous system, while H_4R appears not to be (Haas et al., 2008; Schneider and Seifert, 2016). The initial focus was on H_3R. This receptor couples to G_{alpha}-i and has classically been considered to function primarily as a presynaptic inhibitor of transmitter release, both of histamine itself and of other transmitters (Haas et al., 2008). *Ex vivo*, it has been reported to inhibit DA release (Schlicker et al., 1994). Thus, loss of H_3R tone on DA terminals in KO animals might lead to disinhibited DA release, and HA actions on H_3R receptors on DA terminals might explain the reduced DA seen *in vivo* after HA infusion (Castellan Baldan et al., 2014).

However, recent data argue against this mechanism. The H_3R agonist immepip has not been found to affect intra-striatal DA levels in wild-type mice (Alfaro-Rodriguez et al., 2013). Similarly, systemic administration of the specific agonist R-aminomethylhistamine (RAMH), at doses that produce behavioral effects (see below; Rapanelli et al., in press),

does not produce the predicted reduction in striatal DA – in fact, in KO mice it produces a small but significant elevation in DA after RAMH challenge (Rapanelli et al., in press; Rapanelli et al., 2016). The ability of both endogenous and exogenous HA to reduce striatal DA levels (Castellan Baldan et al., 2014) can be concluded to depend on different receptors.

H_1R is a candidate. H_1R antagonists have been found to acutely increase intrastriatal DA (Dringenberg et al., 1998) and to produce rewarding effects in some behavioral paradigms (Halpert et al., 2002; Zimmermann et al., 1999), although the dependence of such effects on binding to H_1R has been questioned (Oleson et al., 2012; Suzuki et al., 1999). The detailed mechanisms of HA regulation of striatal DA remain an important open question.

Elevated striatal DA is expected to produce a number of secondary effects. First, DA can activate of D_1R -expressing dMSNs. Expression of the immediate early genes *c-fos* was modestly elevated at baseline in the striatum in *Hdc*-KO mice (Castellan Baldan et al., 2014), consistent with such an effect – and perhaps paralleling the dysregulation of the cortico-striatal circuitry seen in patients with TS (Leckman et al., 2010). *C-fos* is elevated following amphetamine challenge, as one would expect; interestingly, *c-fos* expression is particularly high in striosomes after amphetamine challenge in the knockout, relative to wild-type controls (Castellan Baldan et al., 2014). This parallels the specific role for striosomal MSN activity in stereotypy/tic generation suggested by *fos*-mapping investigations in wild-type mice (Canales and Graybiel, 2000).

Elevated striatal DA also has specific effects on molecular signaling within MSNs of both the direct and the indirect pathway (Girault, 2012). Selected signaling pathways were examined in *Hdc*-KO mice (Rapanelli et al., 2014). Signaling through the MAPK pathway was elevated in KO mice, consistent with a DA effect in D_1R -expressing MSNs. The kinases Akt and Gsk3beta were relatively dephosphosphorylated, consistent with a DA effect in D_2R -expresing MSNs. Both effects were further amplified by amphetamine treatment (Rapanelli et al., 2014). These results should be interpreted as preliminary; in particular, these initial studies did not differentiate between MSNs of the direct and indirect pathways. Work to better elucidate specific signaling alterations in these two pathways is ongoing. Additionally, the same pathways can be regulated by postsynaptic H_3R receptors (Rapanelli et al., 2016); this complication is further addressed below.

A third effect of tonic elevation of striatal DA is the development of compensatory changes in DA receptor expression. In particular, treatment with both DA agonists and psychostimulants leads to decreased expression of D_2R receptor in the dorsal striatum and elevated expression of the D_3R receptor in the substantia nigra (Fauchey et al., 2000; Stanwood et al., 2000; Volkow et al., 2009). D_2R and D_3R receptors were examined in *Hdc*-KO mice using *in vitro* binding with the agonist raclopride. D_2R/D_3R receptor binding was downregulated in dorsal striatum, though the effect was subtle. More dramatic was the upregulation of D_2R/D_3R binding in the substantia nigra in KO mice (Castellan Baldan et al., 2014). These alterations are consistent with the predicted effects of chronic DA excess.

Importantly, while striatal DA levels cannot be directly assessed in humans, DA receptors can be. D_2R/D_3R receptors were examined in TS patients carrying the *Hdc* W317X mutation

using positron emission tomography (PET) imaging with the agonist tracer PHNO. This investigation was limited to adult patients; after controlling for imaging quality, 3 adult carriers of the *Hdc* W317X mutation, and 9 matched healthy controls were included in this analysis. In this limited sample, there was no detectable alteration in striatal D_2R/D_3R binding. In the substantia nigra, in contrast, there was a striking upregulation of D_2R/D_3R receptor binding (Castellan Baldan et al., 2014). A similar pattern of increased PHNO binding in the nigra has been seen in human cocaine abusers, supporting the idea that it is a consequence of chronic DA receptor hyperstimulation (Matuskey et al., 2015; Payer et al., 2014). PHNO binding in the substantia nigra is thought to primarily reflect D_3R receptor density (Rabiner et al., 2009; Tziortzi et al., 2011), although it cannot be concluded with complete certainty that the observed increase in PHNO binding is due solely to increased D_3R expression. Regardless, the parallel increase in D_2R/D_3R binding in these patients and in *Hdc*-KO mice adds an additional validation of the mice as an informative model of pathophysiology (Figure 3).

Pathophysiological mechanisms in the *Hdc*-KO model: Histamine receptors

HA receptors have been previously examined in *Hdc*-KO mice; for example, H_3R receptors have been reported to be downregulated in hippocampus and upregulated in hypothalamus in these animals (Chepkova et al., 2012). All four HA receptors were examined in the basal ganglia, using both radioligand binding and *in situ* quantification of mRNA expression (Frick et al., 2016; Rapanelli et al., in press). H_2R receptors are decreased in the striatum in *Hdc*-KO mice, at the level of ligand binding, but not of mRNA expression; this suggests post-translational regulation of receptor level, alteration in affinity rather than expression, or decreased expression on afferents (with the corresponding mRNA alterations elsewhere in the brain). H_4R receptors are also decreased, at the level of both mRNA and ligand binding; this alteration is further addressed below. H_1R receptor are unchanged (Frick et al., 2016; Rapanelli et al., in press).

H_3R receptors are increased in KO mice (Rapanelli et al., in press). H_3R receptors have high constitutive activity, at least in histaminergic neurons themselves (Morisset et al., 2000). This raises the intriguing possibility that elevated H_3R expression may influence striatal function in KO mice even in the absence of its ligand, HA. Systemic administration of the H_3R agonist RAMH produced stereotypies in KO mice. The same effect is produced by the chemically dissimilar agonist immepip; it is blocked by the H_3R antagonist JNJ5207852, further confirming the specificity of the effect (Rapanelli et al., in press). These observations provide further support for the idea that H_3R activity contributes to tic-like phenomenology in these mice.

As noted above, H_3R has classically been considered a presynaptic receptor negatively regulating transmitter release (Haas et al., 2008; Schlicker et al., 1994); and indeed there is evidence for such a role on glutamatergic afferents to the striatum (Ellender et al., 2011). However, it is increasingly evident that postsynaptic H_3R receptors play a prominent and complex role in the striatum (Bolam and Ellender, 2015; Panula and Nuutinen, 2013). Postsynaptic H_3R receptors interact physically and functionally with both D_1R and D_2R

receptors, and their signaling properties are markedly different in different MSN types (Ferrada et al., 2008; Ferrada et al., 2009; Moreno et al., 2011).

These observations were confirmed and extended in MSNs *in vivo*, in wild-type mice (Rapanelli et al., 2016). After acute challenge with the H_3R agonist RAMH, the MAPK signaling pathway is rapidly and transiently activated in D_1R -expressing dMSNs, but not in D_2R-expressing MSNs of the iMSNs. cAMP-dependent modulation of the key regulatory molecular DARPP-32 is not affected by RAMH in either cell type; this is surprising in light of the traditional concept of H_3R as a G_{alpha}-i-coupled receptor, which would be expected to reduce cAMP. Regulation of the Akt-GSK signaling pathway is particularly interesting. DA acting on D_2R receptors in iMSNs inhibits Akt, thus dephosphorylating and thereby activating GSK (Beaulieu et al., 2005). H_3R receptor activation recapitulates this effect. In dMSNs, on the other hand, DA has no effect on Akt-GSK signaling, but H_3R activation activates Akt, thereby phosphorylating and inhibiting GSK (Rapanelli et al., 2016). This differential regulation of Akt/GSK signaling in such similar cell types by H_3R may be unique; its importance is a topic of active investigation.

These abnormalities in signaling *in vivo* after RAMH challenge in wild-type mice are similar to the basal abnormalities seen in knockout animals (Rapanelli et al., 2014). These signaling abnormalities may relate to elevated tonic DA, as discussed above. However, since H_3R receptors are upregulated in *Hdc*-KO mice, these changes may also result from constitutive effects of H_3R (presuming that postsynaptic striatal H_3R receptors have the same high constitutive activity that has been reported in other contexts; Morisset et al., 2000). These possibilities are not mutually exclusive; DA elevation and H_3R upregulation may have additive or interactive effects, the details of which have yet to be worked out.

Pathophysiological mechanisms in the *Hdc*-KO model: modulation of microglia

As noted above, convergent evidence suggests an immune or neuroinflammatory contribution to TS, at least in some cases (Elamin et al., 2013; Frick and Pittenger, 2017; Kumar et al., 2015; Lennington et al., 2016; Williams and Swedo, 2015). HA is a regulator of allergic and inflammatory processes, and dysregulation of peripheral inflammatory processes has been extensively investigated in the *Hdc*-KO mice (Ohtsu, 2010). This motivated us to investigate the effects of HA on microglia, the primary inflammatory cells in the brain. Previous *in vitro* investigations of HA regulation of acutely isolated or cultured microglia have produced conflicting results.

These questions were further examined *in vivo*, in wild-type and *Hdc*-KO mice (Frick et al., 2016). HA infusion into the brain *in vivo* leads to an increased density of and marked morphological changes in microglia, particularly in the striatum and hypothalamus (Frick et al., 2016). This appears to be mediated by the H_4R receptor (Frick et al., 2016), which is thought to be expressed on microglia but not on neurons (Schneider and Seifert, 2016). Conversely, in *Hdc*-KO mice, microglia are normal in number but reduced in their ramifications, and the H_4R receptor is downregulated (Frick et al., 2016), suggesting that HA regulation is important under physiological conditions. (Of note, these studies used a relatively crude measure of microglial process density, the optical density of Iba1

immunostaining; while this measure efficiently reveals differences between groups and between conditions, its relationship to microglial functional 'activation' is unclear.)

This latter observation was initially puzzling, as it contrasts with what has been reported in patients with TS: increased activation of microglia, and increased expression of microglial markers (Frick and Pittenger, 2017; Kumar et al., 2015; Lennington et al., 2016). A resolution to this conundrum may be seen in the recent distinction between neuroprotective and inflammatory microglia (Olah et al., 2011). Some *in vitro* studies (Ferreira et al., 2012; Iida et al., 2015), though not all, suggest that HA-stimulated microglia may have a neuroprotective phenotype, and that HA may antagonize the classical inflammatory effects of stimuli such as lipopolysaccharide (LPS). *In vivo*, *Hdc*-KO mice to have a reduction in the fraction of microglia expressing the neurotrophin IGF-1, which is thought to be a marker of such neuroprotective microglia (Frick et al., 2016). This suggests an intriguing hypothesis, which may have pathophysiological significance: that absence of HA in *Hdc*-KO mice may lead to a deficit in neuroprotective microglia and, perhaps, to a consequent dysregulation of neuroinflammatory responses (Frick and Pittenger, 2017).

This hypothesis was tested by administering LPS to *Hdc*-KO mice. As predicted, *Hdc*-KOs showed an overexuberant microglial response to LPS challenge, apparent both in microglial morphology and in the production of the Th1 interleukin IL-1. As a consequence, microglial ramifications, which were reduced at baseline in KOs relative to WT controls, were increased after LPS (Frick et al., 2016). This observation provides a potential explanation for the discrepancy between the apparently quiescent microglia seen at baseline in the KO model and the activated microglia observed *in vivo* and *post mortem* in TS (Kumar et al., 2015; Lennington et al., 2016). With respect to microglial activation, *Hdc* deficiency (and analogous causal factors) may represent a vulnerability factor but may not fully recapitulate the disease state; in patients, who (unlike vivarium-raised mice) are subject to a lifetime of immune challenges, this may interact with viral infections and other pro-inflammatory stimuli to unmask neuroinflammatory dysregulation.

This 'two-hit' model of microglial dysregulation (Frick et al., 2016; Frick and Pittenger, 2017) suggests that face-valid behavioral phenotypes may be more evident after inflammatory challenge – perhaps even that behavioral stereotypy, elevated grooming, or other TS-relevant behavioral pathology might emerge spontaneously in LPS-challenged mice. Tests of this hypothesis to date have been equivocal (unpublished data); this work is ongoing.

Interpreting the *Hdc*-KO model: what human condition(s) are being recapitulated?

Several different lines of analysis in this model system are summarized above, one or more of which may prove to reflect events that are occurring in patients. Analysis in any such model system is best seen as recapitulating aspects of pathophysiology, and not as capturing TS, or any other particularly disease entity, in its entirety. With this caveat, it may be asked which patients are most likely to manifest similar mechanisms.

Patients carrying the *Hdc* W317X mutation all have TS (or at least chronic tics; in one of the two papers describing these patients, one subject was diagnosed with chronic tics rather than

the full syndrome of TS) (Castellan Baldan et al., 2014; Ercan-Sencicek et al., 2010). But, as is typical for TS, most have comorbidities: 4 OCD (2 full syndrome and 2 subclinical); 3 depression; 1 ASD; 3 social phobia; 1 trichotillomania; 1 ADHD. Thus, the mutation is not associated with tics specifically, but rather with a more complex and somewhat heterogeneous clinical syndrome.

Certain abnormalities seen in the *Hdc*-KO model that can be assayed across species are seen in carriers of the W317X mutation: in particular, prepulse inhibition deficits and elevated D_2R/ D_3R binding in the substantia nigra (Castellan Baldan et al., 2014). But it remains possible that findings in the *Hdc*-KO model will generalize only to patients with this or similar rare mutations affecting brain histamine. Such limited generalizability would obviously reduce the clinical impact of work in the model. Alternatively, findings from the *Hdc*-KO system may generalize to some or all patients with tics, or more broadly, to OCD, ADHD, or other related conditions. This is, ultimately, an empirical question, which has yet to be resolved. The answer may differ for distinct findings in the model system: for example, some candidate pathophysiological mechanisms identified in the model may be seen only in patients with tics; others may be seen in a broader range of clinical groups; and still others may have no relevance to human disease at all.

Closing the loop: testing hypotheses from the Hdc-KO model in patients

The foregoing discussion reemphasizes that, from a translational perspective, such a model system is best considered a generator of pathophysiological hypotheses for testing in humans, and not as a veridical recapitulation of a particular disease or syndrome in its entirety. Ultimately, the translational value of such a pathophysiological model lies in its ability to generate hypotheses about human disease that would not otherwise have been considered, with the ultimate goal of advancing disease diagnosis, treatment, or prevention. With this in mind, it is important to identify abnormalities in the *Hdc*-KO mouse system (and especially in *Hdc* heterozygotes) that are testable in humans.

One of these is shown in Figure 2: elevated D_2R/D_3R availability can be measured *in vivo* in humans using ^{11}C-PHNO PET imaging, and patients carrying the W317X mutation have an abnormality that parallels that seen in the KO mice (Castellan Baldan et al., 2014). It remains to be seen whether a similar abnormality is seen in patients with TS or tics more generally. The fact that similarly increased nigral D_2R/D_3R binding is seen in cocaine users (Matuskey et al., 2015; Payer et al., 2014) suggests that this may be a marker of chronic DA receptor hyperstimulation (Fauchey et al., 2000; Stanwood et al., 2000), and not of tic pathophysiology specifically: that is, elevated PHNO binding may be informative with regard to mechanism, but of limited clinical specificity.

Two other of the findings described above are potentially amenable to *in vivo* testing using PET imaging in humans. First, H_3R upregulation in the striatum, which is seen in the *Hdc*-KO mice and may be of importance in the generation of their repetitive behavioral pathology (Rapanelli et al., in press), can be assayed in humans using the PET ligand ^{11}C-GSK189254 (Gallezot et al., 2016). This has not yet been done in patients with TS, OCD, or related conditions. Interestingly, the H_3R gene is nominally upregulated in post-mortem tissue from

adults with TS, though not to a degree that emerges with statistical significance from the limited studies that have been reported to date (Lennington et al., 2016, supplemental data).

Another finding from the *Hdc*-KO model that can be tested in patients, in principle, is the activation of microglia seen after inflammatory challenge (Frick et al., 2016); this can be tested using *in vivo* PET imaging with the radioligands ^{11}C-PBR28 (Sandiego et al., 2015) or ^{11}C-PK11195 (Kumar et al., 2015), which bind to markers of microglial activation. Indeed, imaging in children with TS using ^{11}C-PK11195 has revealed elevated binding in the basal ganglia, relative to healthy adult controls (Kumar et al., 2015). Further studies will be needed to establish the generality of this abnormality.

Clinically, one ultimate translational goal of such a model is the ability to identify novel therapeutic targets. One candidate target emerges from the studies described above: the histamine H_3R receptor (Rapanelli and Pittenger, 2016). It is not yet clear how the H_3R receptor might best be modulated to mitigate tic-like stereotypy; but the ability of an H_3R agonist to elicit repetitive behavioral pathology in the *Hdc*-KO system (Rapanelli et al., in press) suggests that H_3R antagonism might be therapeutic. Indeed, one recent clinical study has investigated the efficacy of an H_3R antagonist/inverse agonist, AZD5213. Surprisingly, in this small clinical trial, H_3R antagonism produced a small but statistically significant worsening of tics (www.clinicaltrials.gov:NCT01904773). This supports the relevance of the H_3R receptor for the pathophysiology of TS beyond the original W317X family, but it indicates that further work is needed to clarify how this receptor might best be targeted to produce therapeutic benefit.

Conclusion

The association of HA dysregulation with TS and related conditions emerged only recently. Mechanistic work focusing on disease-relevant abnormalities in the *Hdc*-KO model has advanced significantly but remains in its early stages. The initial validation of the model has been summaized (Castellan Baldan et al., 2014), and recent advances in three areas have been described: dopamine dysregulation and abnormalities in DA receptors; abnormalities in HA receptors, especially in H_3R; and dysregulation of microglia and neuroinflammatory processes. Many questions remain in each of these domains.

Most importantly, the translation of these observations back to clinical subjects is incomplete. In the coming years, it is to be hoped that pathophysiological hypotheses generated in the *Hdc*-KO system, and related models, will be testable in patients, and will lead to new insights into the fundamental nature of tic disorders and to new strategies for mitigation or prevention.

Abbreviations

ADHD	attention deficit hyperactivity disorder
Akt	Ak-thymoma protein kinase, also known as protein kinase B

ASD	autism spectrum disorder
AZD5213	an H_3R antagonist
C57Bl/6	C57 Black-6 inbred mouse line
cAMP	cyclic adenosine monophophate
CNV	copy number variation
D_1R	dopamine D_1 receptor
D_2R	dopamine D_2 receptor
DA	dopamine
DARPP-32	dopamine- and cAMP-regulated phosphoprotein
dMSN	direct/striatonigral pathway medium spiny neuron
GABA	gamma-aminobutyric acid
GPe	globus pallidus, pars externa
GPi	globus pallidus, pars interna
GSK3beta	glycogen synthase kinase 3-beta
^{11}C-GSK189254	an H_3 receptor PET tracer
GWAS	genome-wide association study
H_1R	histamine H_1 receptor
H_2R	histamine H_2 receptor
H_3R	histamine H_3 receptor
H_4R	histamine H_4 receptor
HA	histamine
Hdc	*histidine decarboxylase* gene
***Hdc*-KO**	*histidine decarboxylase* knockout mouse
IGF-1	insulin-like growth factor 1
IL-1	interleukin 1
iMSN	indirect/striatopallidal pathway medium spiny neuron
JNJ5207852	an H_3R receptor antagonist
LPS	lipopolysaccharide
MAPK	mitogen-activited protein kinase

mRNA	messenger ribonucleic acid
MSN	medium spiny neuron
OCD	obsessive-compulsive disorder
PANDAS	pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus*
^{11}C-PBR28	a PET tracer that binds to the peripheral benzodiazepine receptor, PBR, a marker of activated microglia
PET	positron emission tomography
PHNO	(+)-4-propyl-9-hydroxynaphthoxazine
^{11}C-PK11195	PET tracer that binds to activated microglia
PPI	prepulse inhibition
RAMH	R-aminomethylhistamine
SMA	supplementary motor area
SNc	substantia nigra, pars compacta
SNr	substantia nigra, pars reticulata
STN	subthalamic mucleus
Th1	Type-1 T-helper cell
TS	Tourette syndrome

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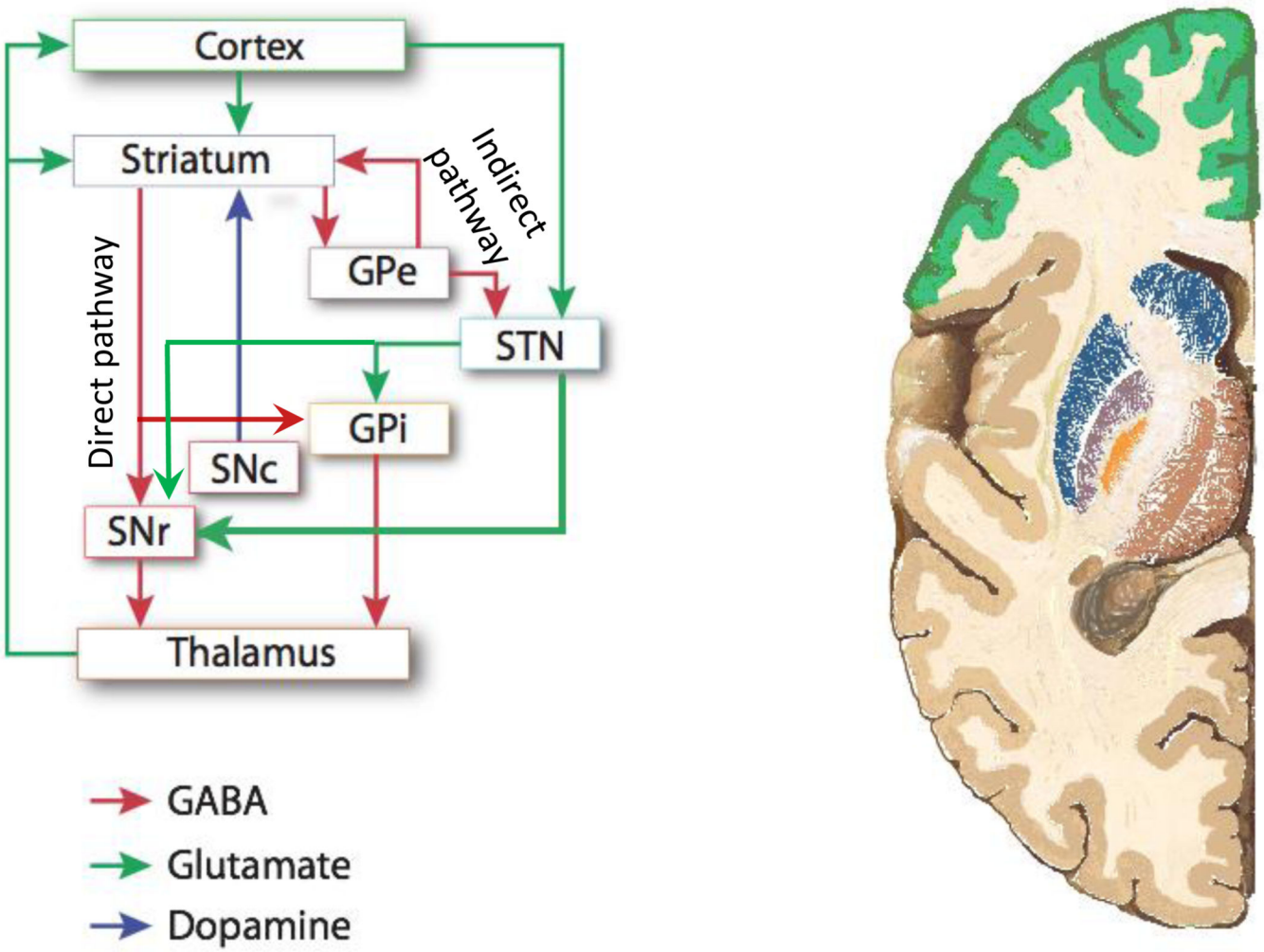

Figure 1. Major pathways through the cortico-basal ganglia circuitry

Dysregulation of the cortico-basal ganglia circuitry is implicated in TS and tic disorders, as well as in OCD and related conditions (Leckman et al, 2010; Maia et al, 2008; Pittenger, 2017). Projections from the cortex and thalamus through the nuclei of the basal ganglia can be conceptualized as traversing two pathways: the direct pathway, which polysynaptically disinhibits thalamic feedback to cortex, and the indirect pathway, which polysynaptically inhibits this feedback. Balance between these two pathways is regulated by dopamine and, perhaps, by histamine. In the *Hdc*-KO model of TS pathophysiology (and, it is proposed, in TS and tic disorders in humans), both DA dysregulation and HA deficiency lead to hyperactivity in the direct pathway and hypoactivity in the indirect pathway; the latter, in particular, may lead to deficient inhibition of off-target action patterns, which may manifest as tics and other repetitive behaviors. See text for further details. Adaptd from Pittenger, Bloch, and Williams, 2011.

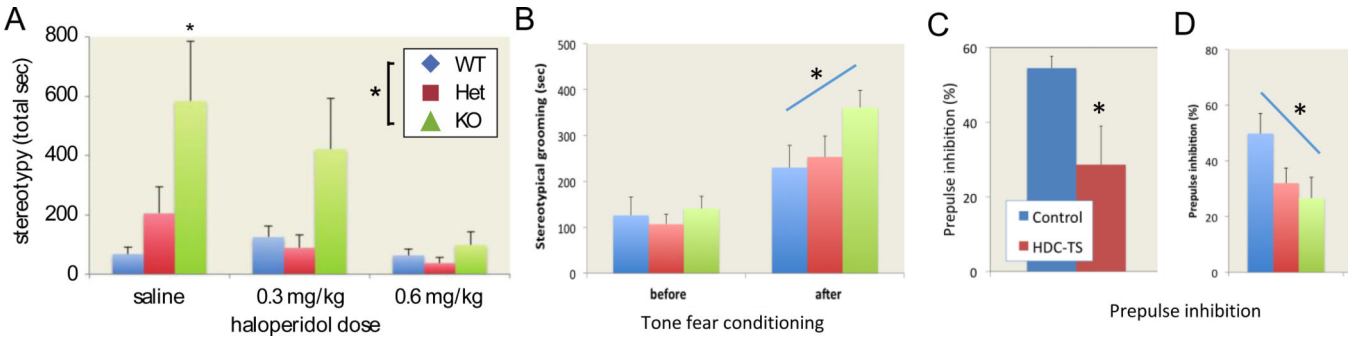

Figure 2. Stereotypies in *Hdc* KO mice

A. Stereotypies after D-amphetamine (8.5 mg/kg) were potentiated in *Hdc* KO and Het mice; pretreatment with haloperidol mitigated this effect. From Castellan Baldan et al, 2014, with permission. **B**. Stress, induced by tone fear conditioning, similarly increased stereotypical grooming. Adapted from Xu et al, 2015b. **C**. Prepulse inhibition (PPI), a measure of sensorimotor gating, was reduced in human carriers of the *Hdc* W317X mutation. **D**. PPI is similarly reduced in *Hdc* heterozygotes and knockouts. Data are shown for a 6 dB prepulse; similar effects were seen with larger prepulses. **C** and **D** from Castellan Baldan et al, 2014, with permission.

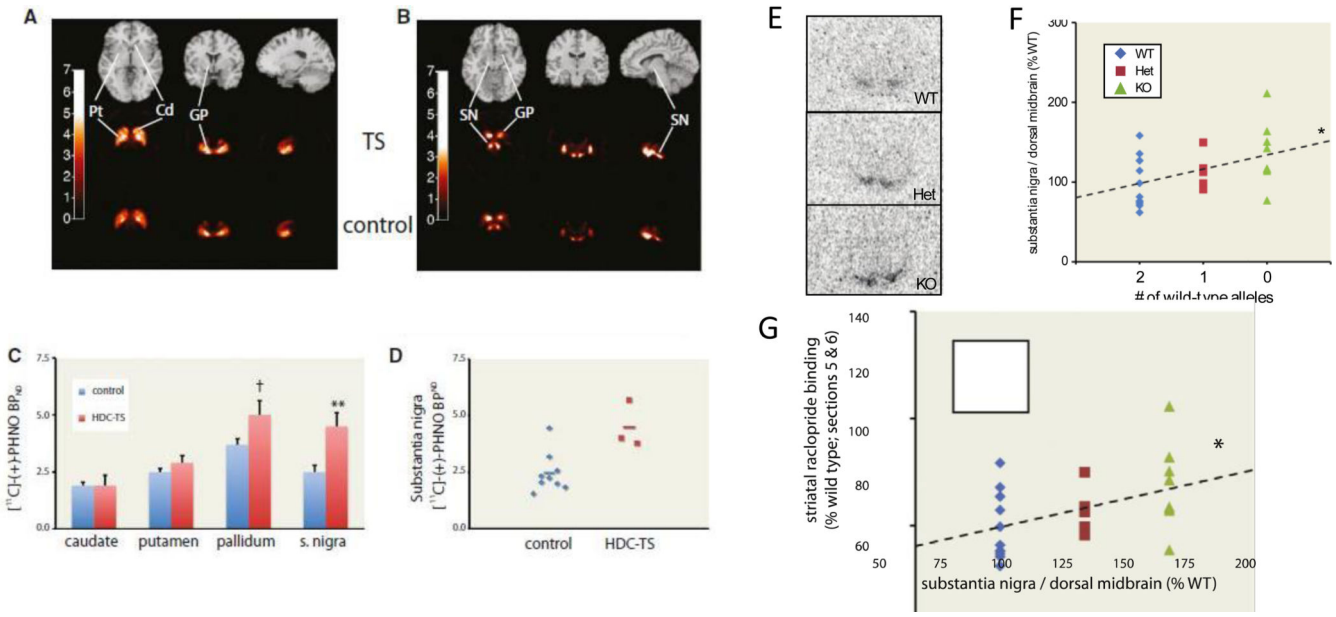

Figure 3. D2/D3 receptors in humans and mice with a mutated *Hdc* gene

A–D. D2/D3R receptor availability in TS patients carrying the *Hdc*-W317X mutation, relative to matched controls, measured using *in vivo* ^{11}C-PHNO PET imaging. **A,B** composite radioligand binding images from patients (middle row) and controls (bottom row). **C**. Binding in subnuclei of the basal ganglia. **D**. Individual subject binding in the substantia nigra in patients and controls; group means are show by a horizontal line. **E-G**. D2/D3R receptor binding in mice measured *ex vivo* using ^{3}H-raclopride binding. **E** Raclopride binding in the substantia nigra. **F**. Increased binding was seen in *Hdc* het and KO mice; individual data are shown. **G**. Reduced raclopride binding was seen in dorsal striatum; this correlated negatively, on an animal-by-animal basis, with the increased binding in the nigra. From Castellan Baldan et al, 2014, with permission.

Characteristic	Patients w/ *Hdc* W317X mutation	*Hdc*+/− & −/− mice	References
Histamine biosynthesis	Reduced (*in vitro*)	Reduced in tissue and striatal microdialysate	Ercan-Sencicek et al, 2010; Castellan Baldan et al, 2014; Ohtsu et al, 2001
Tics/stereotypy	Motor, phonic tics	Potentiated stereotypy after threshold-dose amphetamine and after stress	Ercan-Sencicek et al, 2010; Castellan Baldan et al, 2014; Xu et al, 2015b
Prepulse inhibition	Reduced	Reduced	Castellan Baldan et al, 2014
Striatal dopamine	Not directly measured	Increased in active-phase microdialysate	Castellan Baldan et al, 2014; Rapanelli et al, 2014
Striatal dopamine signaling	Not directly measured	Increased striatal *Fos* expression at baseline and after amphetamine	Castellan Baldan et al, 2014; Rapanelli et al, 2014
Substantia nigra D2/D3 binding	Increased by *in vivo* PHNO PET imaging	Increased by *in vitro* raclopride binding	Castellan Baldan et al, 2014
Dorsal striatal D2/D3 binding	No evident change, by *in vivo* PHNO PET imaging	Modest decrease, by *in vitro* raclopride binding	Castellan Baldan et al, 2014