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Invited Review

Histaminergic modulation in Tourette syndrome

Joanna H. Cox¹, Stefano Seri^{2,3}, Andrea E. Cavanna^{2,4,5*}

¹Heart of England NHS Foundation Trust, Birmingham, UK

²School of Life and Health Sciences, Aston Brain Centre, Aston University, Birmingham, UK

³Children's Epilepsy Surgery Programme, The Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK

⁴Department of Neuropsychiatry, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK

⁵Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology and UCL, London, UK

***Correspondence:**

Prof Andrea E. Cavanna, MD PhD FRCP

Department of Neuropsychiatry

The Barberry National Centre for Mental Health

25 Vincent Drive

Birmingham B15 2FG

United Kingdom

Email: a.e.cavanna@bham.ac.uk

Tel: +44 121 3012280

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Abstract

Introduction. Tourette syndrome is a neurodevelopmental disorder characterized by multiple motor tics and at least one vocal/phonic tic. Clinical phenotypes show a wide variability, often incorporating behavioral symptoms. The exact pathophysiology of Tourette syndrome is unknown, however genetic vulnerability and alterations in dopaminergic neurotransmission have consistently been reported. Other biochemical pathways, including histaminergic neurotransmission, are likely to be involved but have received relatively little attention until recently.

Areas covered. We conducted a systematic literature review focusing on the role of histaminergic neurotransmission and its pharmacological modulation in Tourette syndrome. We identified a number of relevant original studies published over the last five years, mainly focusing on genetic aspects.

Expert opinion. There is converging evidence from recent studies supporting the hypothesis that histaminergic neurotransmission may play a role in the pathophysiology of Tourette syndrome. Most studies focused on the role of the histidine decarboxylase gene and the potential usefulness of histidine decarboxylase knockout mice as an experimental model for studying neurochemical function in Tourette syndrome. There have been no large scale studies assessing the use of histaminergic medications in the management of Tourette syndrome. This would be an important area for future research, with direct implications for the clinical management of selected phenotypes.

Keywords: histamine, Tourette syndrome, tics, animal models, treatment

1. Introduction

1.1. Tourette Syndrome

Tourette syndrome (TS), first described in the medical literature by French neurologist Georges Gilles de la Tourette in the second half of the XIX Century, is a neurodevelopmental disorder characterized by chronic motor and vocal tics [1-4]. Tics are defined as sudden, repetitive, non-rhythmic, involuntary movements and vocalizations [5]. The most common motor tics include eye blinking, facial grimacing, neck stretching, and shoulder shrugging, whereas vocal tics - more appropriately referred to as phonic tics as vocal chords are not always involved - are mainly represented by grunting, sniffing, and throat clearing [6]. Interestingly, tics are characteristically preceded by subjective urges which are relieved by tic expression and can be resisted only for a limited length of time, at the expense of mounting inner tension [7-12]. According to the DSM-5, diagnostic criteria for TS focus on the presence of multiple motor tics plus at least one vocal tic, with onset before the age of 18 years and lasting for over a year [13]. Based on epidemiological studies mainly carried out in school-age children, TS is thought to affect between 0.3% and 0.9% of the population, with a male-to-female ratio of 3-4:1 [6,14,15]. Onset is typically in early childhood; one large multicenter study reported a mean age of onset of 6.4 years [16]. A considerable proportion of patients experience a decline in both the frequency and severity of their symptoms as they enter adult life [17]. Around 90% of patients with TS are diagnosed with co-morbid psychiatric disorders [16,18,19]. The most common behavioral co-morbidities are obsessive-compulsive disorder [20,21] and attention deficit and hyperactivity disorder [22,23], although affective disorders [24] and impulse control disorders [25-27] have been reported more commonly in patients with TS than in the general population.

The exact pathophysiological mechanisms underlying TS are unknown, however converging lines of evidence point to abnormally increased dopamine neurotransmission, particularly at the level of the basal ganglia and fronto-striatal circuitries [2,28-30]. This hypothesis is in line with evidence of altered structural connectivity within the cortico-striato-pallido-thalamic circuitry [31]. As with other neurodevelopmental conditions, there is solid evidence for a genetic component to the expression of TS [32,33], thought to involve complex multigene changes [34]. TS has a heritability of approximately 0.58 [35] and its genetic heterogeneity has recently been confirmed by the results of recent large studies, which have failed to identify a single shared mutation or even common polymorphisms [36].

Environmental factors also play a role and autoimmune mechanisms have been proposed to be involved at least in a subgroup of patients [37,38].

A proportion of patients with TS do not require intervention, however when tics and/or comorbid behavioral problems are considered physically, socially or emotionally disabling and cause functional impairment, active treatment can be implemented [39]. Management of TS is primarily pharmacological [39,40], although behavioral therapies [41,42] and neurosurgical interventions [43-45] have shown benefit in selected patients. Pharmacological agents belonging to a number of classes are routinely used in the treatment of TS, the most commonly prescribed being dopamine antagonists [46]. First-line treatment options often include either an alpha-adrenergic agonist such as clonidine [47] or atypical antipsychotic agents such as risperidone and aripiprazole [39]. Second-line options include old generation or typical neuroleptics, such as haloperidol and pimozide, with established efficacy but worse tolerability profiles [48]. In a number of cases polypharmacy is needed, alongside behavioral interventions, such as habit reversal training [49,50], and, in refractory cases, deep brain stimulation [43-45].

1.2. Dopaminergic and Histaminergic Pathways in Tourette Syndrome

Although the majority of studies have supported the role of dopamine in TS, there is growing evidence for alterations across multiple biochemical systems [51,52], including abnormal histaminergic neurotransmission [53]. Histamine is an organic nitrogenous compound that acts as a signaling molecule in the immune and gastrointestinal systems, as well as a neurotransmitter within the central nervous system [54]. Histaminergic neurons mainly originate from the tuberomammillary nucleus of the hypothalamus [55], and their widespread projections reach most areas of the brain. Histamine acts through four receptors (H1-H4) and actively regulates arousal, feeding, learning and memory processes [56,57]. H1 and H2 receptors are expressed throughout the central nervous system, H3 receptors are limited to the brain, and H4 receptors are primarily located in the immune system, with limited action on the brain [58,59]. Specifically, H3 receptors are found in high concentrations throughout the cortex, hippocampus and striatum [54], the latter of which has been strongly associated with TS pathophysiology. Moreover, H3 receptors in the striatum have been shown to have significant roles in modulating dopaminergic neurotransmission [59,60], thus further supporting their possible role in TS [61]. Specifically, histamine neurotransmission appears to reduce the concentration of dopamine in the striatum by acting at H3 heteroreceptors on dopaminergic afferents. Through this action, histamine can exert control on the dopaminergic pathways targeting the GABAergic medium-spiny projection neurons that make up approximately 95% of all striatal neurons, thereby affecting the behaviour of the basal ganglia as a whole.

1.3. Histaminergic Neurotransmission and Neuropsychiatric Disorders

Alterations in histaminergic pathways are known to have far-reaching consequences and it is therefore not surprising that histamine neurotransmission has been implicated in a number of neurological conditions [62-66]. For example, in post-mortem studies of patients with Alzheimer disease, levels of histamine were reduced in the hypothalamus, hippocampus and temporal lobes when compared to controls [67]. Histamine has also been shown to decrease neurotoxicity produced by β -amyloid in Alzheimer disease, a process that appears to be regulated by the H2 and H3 receptor subtypes. Overall, H3 receptors have also been implicated in suppressing histamine release in the brain. Therefore, pharmacological agents known to antagonize the H3 receptor and to regulate the H2 receptor have been proposed as promising treatment avenues for patients with Alzheimer disease [68]. Likewise, reduced histamine levels have also been demonstrated after bilateral carotid artery occlusion in rats, suggesting a potential role in vascular dementia [69]. Furthermore, patients with Parkinson disease, but not those with more severe forms of 'Parkinson-plus' conditions such as multiple system atrophy, were found to have increased levels of brain histamine [70]. Finally, low histamine levels have been documented in patients with epilepsy and H3 receptor blockade (which increases endogenous brain histamine release) has been reported to increase seizure threshold [71]. Studies investigating the role of other histamine receptors have produced mixed results [72].

1.4. Systematic Literature Review

This article will systematically review the current evidence for the role of histaminergic neurotransmission in TS. In order to comprehensively identify relevant articles within this dynamic research area, the PRISMA guidelines for reporting systematic literature reviews [73] were followed. Both PubMed and PsycInfo databases were searched using the search

terms *tourett** OR *tic** AND *histamin** and limited to English language. After removing duplicates and studies not focusing on histamine and/or TS, the authors manually screened the abstracts of the remaining articles for relevance to histaminergic neurotransmission in TS, and identified the studies that are included in this review.

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2. Tourette Syndrome and Histaminergic Neurotransmission

2.1. Clinical Studies

A small number of original studies have been carried out to specifically investigate the role of histamine neurotransmission in TS. A genetic linkage study carried out on a family with an unusually high prevalence of TS provided initial evidence of a possible role of histaminergic dysfunction [74]. DNA samples from all family members in the two-generation pedigree were obtained and genotyped. The father and all eight offspring met the DSM-IV-TR diagnostic criteria for TS [75], whereas the mother and extended family were apparently free from tics or other symptoms of TS. In terms of TS-related behavioral symptoms, the father and two children also had obsessive-compulsive disorder. This family showed a Mendelian pattern of autosomal dominant inheritance, which is rarely seen in TS. Polymerase chain reaction (PCR) analyses identified a premature termination codon (W317X) on exon 9 of the histidine decarboxylase (HDC) gene, which was present in the father and offspring, but absent in the mother. This termination codon resulted from a guanine-to-adenosine transition at the nucleotide 951 position of the gene, leading to a complete loss of enzyme function. The HDC gene codes for the enzyme histidine decarboxylase, a rate-limiting enzyme in the biosynthesis of histamine from L-histidine [53]. These findings therefore suggested a potential role for HDC deficiency in the pathophysiology of TS through impairment of histamine neurotransmission. However, the inheritance pattern in this family is uncommon for TS, and a mutation screening of Chinese Han patients did not support the link between the aforementioned gene and TS [76].

In 2012, a case-control study of 460 patients with TS focused on copy number variants (CNVs) to identify risk regions or molecular pathways which may be associated with TS [77]. The authors found no statistically significant increase in CNVs when comparing

patients with TS to controls, however there was some overlap between CNVs found in patients with TS and those previously identified in autism spectrum disorder. Moreover, pathway analysis showed enrichment of genes within the H1 and H2 receptor signaling pathways. Presynaptic receptors in these pathways regulate release of histamine and of other neurotransmitters such as dopamine, suggesting wider neural signaling abnormalities in TS. A limiting factor of this study was the relatively small sample size compared to similar CNV analyses in other patient cohorts.

The identification of the previously mentioned HDC mutation led to a study in 2013 that investigated variations across the whole HDC gene [78]. This study involved 520 families with TS from seven European Countries. Genotyping studies found strong over-transmission of alleles at two single nucleotide polymorphisms (rs854150 and rs1894236). These results confirmed a putative role for histamine pathways in neuronal development, and provided further support to the hypothesis that dysfunction in these pathways may be involved in development of TS at least in a subgroup of patients.

2.2. The HDC Knockout Mouse Model

HDC deficiency was investigated in a recent study [79] using a HDC knockout model. Although mice which are deficient in the HDC gene do not exhibit detectable tic-like movements at baseline, when challenged with either high-dose psychostimulants or acute stress they develop repetitive purposeless movements (e.g. focused sniffing, orofacial movements, excessive grooming) that may resemble tic symptoms. Clearly no animal model can capture all aspects of the complex phenomenology of TS, however these behavioral phenotypes were thought to be qualitatively different to the increased locomotion upon stimulant administration and amphetamine-induced stereotypies observed in healthy mice.

Interestingly, these tic-like behaviors could be alleviated by repletion of histamine via intracerebral infusion. Furthermore, striatal dopamine levels appeared to be negatively regulated by histamine, as the HDC knockout mice exhibited increased dopamine turnover. In consideration of the known role of increased dopamine neurotransmission in the pathophysiology of TS, these results provided *in vivo* experimental evidence of a direct relationship between histamine and dopamine regulation in the basal ganglia. Interestingly, it was noted that the decrease or disappearance of tics in patients with TS parallels the circadian pattern of histamine. The histaminergic neurons projecting from the tuberomammillary nucleus of the hypothalamus to a wide range of brain structures, including the striatum, fire at high frequency during wakefulness and are virtually silent during sleep. The possibility that histamine exerts a diurnal control on the activity of the basal ganglia circuitry would be in line with the known fluctuations in tic expression (waxing and waning during day time and decrease/remission during night time). The authors of these experiments acknowledged the possibility that the HDC knockout mouse model might be representative of a relatively rare pathophysiological mechanism for TS and that this might therefore be relevant to only a small proportion of patients with TS. However, these findings led to the suggestion that increasing brain histamine could potentially be of therapeutic benefit, and that dietary supplementation with histidine may increase histamine production.

The HDC knockout mouse model was also used in a further study from 2014 analyzing changes in signaling pathways in the striatal cells in comparison to animals [80]. The study found that levels of dopamine were higher in the HDC knockout mice, and there were also alterations to protein kinase B Akt and mitogen-activated protein kinase (MAPK) signaling pathways. The changes discovered in these pathways are characteristic of the effects of dopamine on striatal neurons. Furthermore, the investigators identified glycogen synthase kinase 3 beta (GSK3 β) as a potential therapeutic target due to its role in the AKT pathway.

Since the first reports of a possible association between HDC deficiency and TS, the HDC knockout mice paradigm has been used in multiple studies as an experimental model of TS. This model opened promising avenues, as HDC knockout mice show a phenotype that shares some components with the symptoms of patients with TS [81]. Specifically, the study by Castellan Baldan et al. [79] provided evidence for disturbed sensorimotor gating in HDC knockout mice, as indicated by reduced pre-pulse inhibition (a neurophysiological phenomenon in which a weak pre-stimulus sound inhibits the reaction to a subsequent strong startling stimulus). Reduction in pre-pulse inhibition was also observed in patients with TS carrying the HDC W317X mutation [74], presumably as a result of elevation of striatal dopamine levels [82], which is in turn caused by a lack of inhibitory effect of histamine on dopamine release. This hypothesis was confirmed by the findings of the study by Castellan Baldan et al. [79], who directly determined striatal dopamine using micro-dialysis: during the night-phase, when mice become active, striatal levels of histamine were found to be increased in wild-type mice, but not in HDC knockout mice; conversely, dopamine levels were significantly higher during the night phase in HDC knockout mice as compared to wild-type controls [79]. The inhibitory effect of histamine was further demonstrated by histamine infusion into wild-type mice, resulting in a significant reduction in striatal dopamine compared to saline controls [79]. Finally, both patients with TS carrying the HDC W317X mutation and HDC knockout mice showed an upregulation of dopamine D2 and D3 receptors in the substantia nigra, as determined by positron emission tomography in the patients with TS using ¹¹C-labeled 4-propyl-9-hydroxynaphthoxazine binding or by ³H-raclopride binding to brain slices of HDC knockout mice [79]. Taken together, these findings suggested that HDC knockout mice may represent a valid animal model for human TS, although the tic-like repetitive behaviors (e.g. sniffing-like head movements) observed in HDC knockout mice in the study by Castellan Baldan et al. [79] were not observed at baseline, but emerged after

acute challenge with the psychostimulant amphetamine (and were completely eliminated by pretreatment with either haloperidol or histamine). The fact that amphetamine was necessary to induce a tic-like phenotype in HDC knockout mice brought further evidence to suggest that these animal models are only partly comparable to patients with TS, who display symptoms without pharmacological challenge. A recent study by Xu et al. [83] tested the ability of an acute stressor to stimulate repetitive behaviors in this experimental model using tone fear conditioning. HDC knockout mice acquired conditioned fear normally, as manifested by freezing during the presentation of a tone 48 hours after it had been paired with a shock. During the 30 minutes following tone presentation, knockout mice showed increased grooming, whereas heterozygote mice exhibited normal freezing and intermediate grooming. These data validated a new paradigm for the examination of tic-like repetitive behaviors in animals without pharmacological challenge and enhanced the face validity of HDC knockout mice as a pathophysiologically grounded model of tic disorders.

2.3. Pharmacological Modulation

At present, no large-scale clinical trials of histaminergic modulators have been undertaken in the TS patient population. A preliminary report from 1986 presented a small case series of three patients with TS where use of antihistaminergic agents exacerbated tics [84]. Caution is required when interpreting these findings, also in consideration of the non-selectivity (anticholinergic properties etc.) of antihistaminergic medications in clinical use. More recently, a case report published in 2012 presented the case of a male patient with TS and comorbid narcolepsy [85]. This patient's condition had proven refractory to treatment with a number of antidopaminergic medications. Based on the findings of the study by Ercan-Sencicek et al. [74], the patient underwent a trial with the H3 receptor inverse agonist

pitolisant. The authors found that pitolisant significantly decreased daytime sleepiness without worsening in tic severity, a common side effect associated with other psychostimulants such as methylphenidate and modafinil. However, contrary to what could be expected based on the histamine hypothesis of tics, the administration of pitolisant resulted in no significant improvement in tic severity. The authors considered that the lack of tic worsening in a sensitive patient (who had experienced worsening of tics on both methylphenidate and modafinil) warranted a controlled clinical trial of H3 receptor reverse agonists in patients with TS, particularly in the presence of co-morbid attention deficit hyperactivity disorder. It should be noted however that stimulant medications are not consistently associated with tic exacerbations, especially if administered in lower doses and with gradual titration [86,87]. Further supported by results of a positron emission tomography study assessing the novel H3 receptor antagonist AZD5213 [88], a randomized-controlled trial assessing its use has been undertaken, but as yet no results have been published (ClinicalTrials.gov: NCT01904773).

There is evidence that histamine can directly control striatal neurons by affecting the activity of multiple neurotransmitters which are supposed to play a role alongside dopamine in the pathophysiology of TS [51-53]. Histamine can modulate the intrinsic electrical properties of striatal cholinergic interneurons and negatively regulate the release of GABA from striatal medium-spiny projection neurons by acting at the level of H3 heteroreceptors. Through the same mechanism, histamine can also modulate glutamatergic neurotransmission by decreasing the release of glutamate from striatal synaptosomes and reducing the electrically evoked glutamatergic field responses. Finally, it is possible that the histaminergic action affects other striatal neuromodulatory pathways, such as the noradrenergic and serotonergic pathways, which would allow for complex interactions amongst neuromodulators, thus expanding the spectrum of potential pharmacological targets for TS.

3. Expert Opinion

3.1. Promising Avenues for Research

Our systematic literature review was able to identify a small number of original studies specifically investigating histaminergic neurotransmission in TS. Interest in this topic was first generated by the report that a rare mutation in the HDC gene (W317X) was associated with the occurrence of TS in a two-generation pedigree [74]. Patients with the W317X mutation of HDC are unable to synthesize histamine and depend on the activity of HDC encoded by the non-mutated second allele. The presence of specific psychiatric comorbidities in some male members of this pedigree could also be explained by a dysfunction in the histaminergic system, as overriding inhibition of competing pathways within parallel cortico-striato-thalamo-cortical loops can hinder behavioral switching as seen in obsessive-compulsive disorder [89]. A more general association of histaminergic pathways with TS was identified by analysis of rare CNVs in a subsequent study [77]. The hypothesis of an involvement of the histaminergic system in the pathogenesis of TS was also supported by a more recent report on single nucleotide polymorphisms in the HDC region that are associated with TS [78]. However, HDC mutations were not replicated in larger scale studies [76], suggesting that these genetic alterations may only be responsible for a subset of patients with TS. Interestingly, we have recently seen increasing consensus that TS is a heterogeneous condition from both the phenotypic and genotypic points of view. Studies conducted using principal-component factor analysis [90-95], hierarchical cluster analysis [90,93,94,96] and latent class analysis [97,98] have identified a number of clinical phenotypes which, if replicated, could prompt further research into individual genotype correlates. Perhaps the main limitation in our understanding of the role of histaminergic neurotransmission for the pathophysiology of TS is its limited generalizability, since a significant proportion of patients with TS have not shown any alterations in the HDC gene, indicating that this might be a rare

pattern of TS inheritance. Further exploration of the role of histaminergic transmission in TS might still offer some insight if associated with careful stratification of patients by specific behavioral and intermediate phenotypes within the TS spectrum. Based on the reviewed evidence, these points should stand as key lessons for the industry. In order to increase the knowledge base in this area, further research into other areas of histaminergic neurotransmission should be conducted. Examples may include comparing brain histamine levels in large cohorts of patients with TS and healthy controls, or carrying out further gene identification studies. Functional molecular neuroimaging studies may also provide a promising avenue of research.

If alterations in histaminergic neurotransmission are identified in a large cohort of patients with TS, this might have a significant payback in the design of novel classes of medications that modulate histamine and carry direct therapeutic implications. Based on current evidence, patients with TS associated with HDC deficiency may benefit from pharmacological histamine modulation, particularly involving agents acting on the H3 receptor. Expression of H3 receptors has been reported to be elevated in the HDC knockout model of TS at the level of the basal ganglia [99], a key region for the pathophysiology of TS, as altered striatal histaminergic-dopaminergic tone has been shown to potentially result in tic generation [89]. H3 receptors are thought to be localized primarily presynaptically, both as autoreceptors on histaminergic terminals, where they may play a role in negative feedback regulation of histamine release, and as heteroreceptors on dopaminergic, glutamatergic and cholinergic neurons. Moreover the expression of this receptor is largely specific to the central nervous system, indicating that it could be pharmacologically targeted with minimal concern about peripheral side effects. Although pilot clinical studies in narcolepsy, schizophrenia and attention deficit disorder have yielded mixed results (with more favorable outcomes in conditions characterized by hypersomnia), preclinical evidence strongly suggests that H3

antagonism could open novel therapeutic avenues in TS and other neuropsychiatric disorders [99]. Specifically, the use of H3 antagonists could be assessed either as a monotherapy or in combination therapy for patients already taking medication, with the goal of expanding the relatively narrow range of safe and effective pharmacological options currently available to clinicians treating patients with TS [39,40,100]. Further implications of additional research into this field may include identification of families at risk of TS. Although TS is not known to shorten life expectancy, it can be highly detrimental to patients' health-related quality of life and psychosocial wellbeing [101-103]. Finally, recent observations that patients with TS can be prone to develop allergy related to histamine-associated immunological reactions prompt further investigations into the relationship between allergy, histamine and TS [104].

3.2 Preliminary Conclusions

In conclusion, although the results of a number of small scale studies support the hypothesis that histaminergic neurotransmission may play a role in the pathophysiology of TS, the majority of research has focused on the role of the HDC gene and there have been no large scale studies assessing the use of histaminergic medications in the management of TS. The wide phenotypic heterogeneity that characterizes TS poses as a significant challenge; however recent research has paved the way for further work into the identification of more precise genotype-phenotype correlations. Histaminergic neurotransmission is an area of interest for future research, with potential to impact the management and treatment of patients in the long term.

Declaration of interest

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ACCEPTED MANUSCRIPT

Article Highlights

- Tourette syndrome is a chronic tic disorder traditionally associated with alterations of dopaminergic neurotransmission, although the exact pathophysiology is still unknown.
- Other biochemical pathways, involving histaminergic neurotransmission, are likely to play a role in Tourette syndrome pathophysiology, but have received relatively little attention until recently.
- We identified a number of relevant original studies exploring the possible role of histaminergic transmission in Tourette syndrome, published over the last five years.
- Most studies focused on the role of the histidine decarboxylase gene and the potential usefulness of histidine decarboxylase knockout mice as an experimental model for studying neurochemical function in Tourette syndrome.
- Development and large-scale use of histaminergic medications deserve further research, with direct implications for the clinical management of selected Tourette syndrome phenotypes.