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Research article

Genetic lack of histamine upregulates dopamine neurotransmission and alters rotational behavior but not levodopa-induced dyskinesia in a mouse model of Parkinson's disease

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ABSTRACT

The brain histaminergic and dopaminergic systems closely interact, and some evidence also suggests significant involvement of histamine in Parkinson's disease (PD), where dopaminergic neurons degenerate. To further investigate histamine-dopamine interactions, particularly in the context of PD, a genetic lack of histamine and a mouse model of PD and levodopa-induced dyskinesia were here combined. Dopaminergic lesions were induced in histidine decarboxylase knockout and wildtype mice by 6-hydroxydopamine injections into the medial forebrain bundle. Post-lesion motor dysfunction was studied by measuring drug-induced rotational behavior and dyskinesia. Striatal tissue from both lesioned and naïve animals was used to investigate dopaminergic, serotonergic and histaminergic biomarkers. Histamine deficiency increased amphetamine-induced rotation but did not affect levodopa-induced dyskinesia. qPCR measurements revealed increased striatal expression of D1 and D2 receptor, DARPP-32, and H3 receptor mRNA, and synaptosomal release experiments in naïve mice indicated increased dopamine release. A lack of histamine thus causes pre- and postsynaptic upregulation of striatal dopaminergic neurotransmission which may be reflected in post-lesion motor behavior. Disturbances or manipulations of the histaminergic system may thus have significant consequences for dopaminergic neurotransmission and motor behavior in both healthy and disease conditions. The findings also represent new evidence for the complex interplay between dopamine and histamine within the nigrostriatal pathway.

1. Introduction

In Parkinson's disease (PD), motor impairment is caused primarily by the death of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the subsequent loss of striatal dopamine, although other neurotransmitter systems are affected as well [1]. An effective treatment for the motor symptoms is the dopamine precursor 3,4-dihydroxy-L-phenylalanine, or levodopa [1]. However, the development of motor complications, such as abnormal involuntary movements called levodopa-induced dyskinesia (LID), often complicates treatment [2]. Abnormalities in striatal dopaminergic neurotransmission represent the main mechanism of LID, but other neurotransmitter systems are also involved [2].

Abundant evidence from animal models suggests complex interactions between the dopaminergic and histaminergic systems within the basal ganglia [3]. Furthermore, human nigral histaminergic fibers are in close contact with dopaminergic neurons and show increased innervation and changed morphology in PD [4]. Higher blood and brain levels of histamine and increased histamine H3 receptor (H3R) expression have also been reported in PD patients [5–7]. Finally, treatments with a histamine H2 receptor (H2R) antagonist and a H3R agonist attenuated levodopa-induced abnormal movements in rodent and primate models of PD [8–11].

As the role of central histamine in healthy and especially disease states is still quite unknown, the histaminergic system can thus be seen as a promising but mostly uninvestigated research avenue in the context of PD. Here, a complete lack of endogenous histamine and a parkinsonian mouse model were combined to investigate the role of the histaminergic system in PD and LID. This was achieved by utilizing a mouse line [12] lacking the histamine-synthesizing enzyme histidine decarboxylase (HDC) along with lesioning of the nigrostriatal dopaminergic pathway by intracerebral 6-hydroxydopamine (6−OHDA) injections. The consequences of the histamine deficiency to post-lesion motor behavior were studied by measuring drug-induced rotational

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behavior and LID. Striatal tissue from lesioned animals was then used to measure the mRNA of biomarkers of the dopaminergic system (dopamine receptors 1–2 and DARPP-32, a major postsynaptic signaling molecule), the histaminergic system (the H3R, particularly important in the striatum and in histamine-dopamine interactions [3]), and the serotonergic system (the 5-HT2A receptor, serotonin being involved in the mechanisms of LID [2]). Finally, striatal synaptosomes from naïve animals were used to measure presynaptic dopamine release.

2. Materials and methods

2.1. Animals

Adult (21–27 weeks) female HDC knockout (HDC KO) mice [12] and their wildtype (WT) littermates, fully backcrossed to C57BL/6, were group housed in a temperature- and humidity-controlled environment under a 12 h light/dark cycle. 11 KO and 14 WT mice were used for lesioning, and 6 KO and 5 WT mice for synaptosomal experiments. Experiments were conducted according to the 3R principles of the EU directive 2010/63/EU governing experimental animals and to local regulations, and authorized by the Animal Experiment Board of Finland.

2.2. Mouse model of Parkinson's disease and levodopa-induced dyskinesia

Unilateral nigrostriatal lesions were induced as described previously [13]. In brief, 3 µg 6−OHDA (Sigma-Aldrich, St. Louis, MO) was administered in a stereotactic surgery into the medial forebrain bundle (MFB) at the following coordinates: A/P−1.2, M/L −1.1, D/V–5.0. Desipramine pretreatment was not used. Mice received two weeks of intensive postoperative care [13]. Four mice (2 KO, 2 WT) either died during surgery or were euthanized due to poor condition.

Three weeks after surgery, rotations induced by the dopaminergic drugs amphetamine (2.5 mg/kg, i.p.; Faculty of Pharmacy, University of Helsinki, Finland) and, a week later, apomorphine (0.5 mg/kg, i.p.; Sigma-Aldrich) were measured as described previously [14]. In brief, a modified automatic detector system (Roto-Rat, Med Associates, St. Albans, VA) was used to measure rotations at 5 min intervals. Net ipsi- or contralateral rotations were used in data analysis.

Beginning a week after the rotametry, mice were administered (s.c.) levodopa (4.5 mg/kg; Sigma-Aldrich) and benserazide (1.125 mg/kg; Sigma-Aldrich) once per weekday. After two weeks, the mice were individually recorded for 1 min at 20, 40, 60 and 80 min after the levodopa injection in transparent cylinders flanked by two vertical mirrors. Dyskinesia severity was assessed from randomized recordings in a blinded fashion using previously described scoring criteria [15]. Briefly, dyskinetic behaviors were classified into axial, orolingual and forelimb dyskinesia and rated on a scale of 0–4.

2.3. Ex vivo assays

Lesioned mice were killed with cervical dislocation 3 h after the last levodopa injection. To assess the extent of dopaminergic denervation, the posterior part of the brain was fixed overnight in 4 % paraformaldehyde in PBS, stored in 20 % sucrose in PBS at +4 °C, and used for tyrosine hydroxylase (TH) immunohistochemistry in 30 µm free-floating coronal brain sections as described previously [16] with the exception that the secondary antibody was replaced with biotinylated protein A. Stained sections were imaged using a 3DHISTECH slide scanner (3DHISTECH, Budapest, Hungary), and optical density across the SNc was measured as described previously [15]. Results were expressed as percent of intact side, and the lesion extent for each mouse was calculated as the mean of three consecutive sections.

In the same lesioned mice, tissue samples from the dorsal striatum of both hemispheres were used for qPCR assays of mRNA for the dopamine 1 receptor (D1R), dopamine 2 receptor (D2R), dopamine- and cAMP-regulated phosphoprotein, 32-kDa (DARPP-32), H3R and the serotonin 5-HT2A receptor as described previously [14]. The following TaqMan hydrolysis probes (Applied Biosystems, Foster City, CA) were used: D1R, Mm02620146_s1; D2R, Mm00438545_m1; DARPP-32, Mm00454892_m1; H3R, Mm00446706_m1; 5-HT2A, Mm00555764_m1. GAPDH (Mm99999915_g1) and PPIA (Mm02342430_g1) were used as reference genes.

For synaptosomal [^{3}H]dopamine release studies, fresh striatal tissue was collected from naïve mice. Preparation of striatal synaptosomes, uptake of [^{3}H]dopamine (PerkinElmer, Waltham, MA), superfusion of synaptosomes for 10 min, collection of 10 s superfusate fractions, and measurement of released radioactivity were performed as described previously [17], with the exception that nomifensine was not added to the superfusion buffer. Release was stimulated for 20 s by either adding amphetamine (0.5 or 10 µM) to the superfusion buffer or, to study depolarization-stimulated release, raising its KCl concentration to 20 mM. Release data were analyzed as previously described [15].

2.4. Statistical analysis

Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA). Rotametry and LID data were analyzed with repeated measures analyses of variance (RM ANOVA) with Greenhouse-Geisser correction (sphericity not assumed) and Sidak's *post hoc* tests. Data from qPCR and optical density measurements were analyzed with two-way ANOVA. Results of [^{3}H]dopamine release from striatal synaptosomes were analyzed with two-way ANOVA and an unpaired *t*-test.

3. Results

3.1. Immunohistochemical characterization of SNc dopaminergic lesions

Optical density measurements in midbrain sections immunostained for TH were used to quantify the extent of dopaminergic neurodegeneration in the SNc (Fig. 1). Three WT and one KO mice were excluded from all data analyses due to unsuccessful lesioning (defined as more than 33 % SNc TH remaining). Lesion extent did not differ between HDC KO and WT mice.

3.2. Drug-induced rotational behavior and dyskinesia in histamine-deficient mice

To evaluate differences in hemiparkinsonian motor imbalance between unilaterally lesioned HDC KO and WT mice, rotations induced by indirect and direct dopaminergic agonists (amphetamine and apomorphine, respectively) were measured (Fig. 2A). Amphetamine-induced rotational behavior was significantly increased in HDC KO mice (genotype effect: $F_{1,15} = 9.023$, $p = 0.0089$; genotype x time interaction: $F_{17,255} = 2.258$, $p = 0.0036$). However, apomorphine-induced rotational behavior did not significantly differ between genotypes. Subsequently, abnormal movements induced by repeated levodopa administration were measured to evaluate any differences in LID expression (Fig. 2B). One successfully lesioned KO mice was excluded due to not developing dyskinesia. No statistically significant genotype differences in dyskinesia severity were observed.

3.3. Biomarkers of neurotransmitter function in histamine-deficient mice

mRNA expression was measured with qPCR from striatal tissue samples from unilaterally lesioned mice (Fig. 3A). The expression of four of the investigated markers (D1R, D2R, DARPP-32, H3R) was significantly increased in HDC KO mice (D1R genotype effect: $F_{1,30} = 5.45$, $p = 0.0264$; D2R genotype effect: $F_{1,30} = 4.69$, $p = 0.0384$; DARPP-32 genotype effect: $F_{1,06} = 6.050$, $p = 0.0203$; H3R genotype effect: $F_{1,30} = 5.902$, $p = 0.0213$). 5-HT2A mRNA was

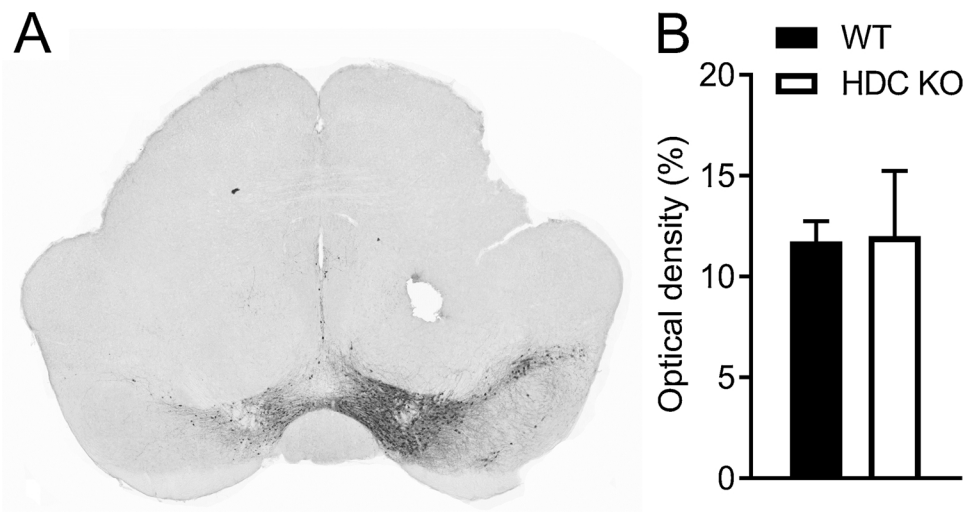

Fig. 1. Extent of dopaminergic denervation in the 6-hydroxydopamine model. A: A representative section, immunostained for tyrosine hydroxylase, showing a typical lesion of the ventral midbrain dopaminergic areas achieved with a 6−OHDA injection into the medial forebrain bundle. **B**: Quantification of the remaining SNc immunostaining in wildtype and HDC KO mice. Mean optical density + SEM shown, $n_{WT} = 9$, $n_{KO} = 8$.

expressed similarly between genotypes. The dopaminergic lesion had no statistically significant effects on mRNA expression.

Striatal synaptosomes from naïve HDC KO and WT mice were used to study both amphetamine-induced and depolarization-stimulated release of [^{3}H]dopamine. Depolarization-stimulated [^{3}H]dopamine release (Fig. 3B) was significantly increased in HDC KO animals ($t(9) = 3.382$, $p = 0.0081$), but neither half-maximal (0.5 μM) nor maximal (10 μM) amphetamine-induced [^{3}H]dopamine release (Fig. 3C) differed between HDC KO and WT mice.

4. Discussion

The histaminergic and dopaminergic systems interact closely within the basal ganglia, and the histaminergic system could play a significant role in conditions of dopaminergic dysfunction such as Parkinson's disease and levodopa-induced dyskinesia [3–7]. Here, the role of histamine in PD and LID was studied by investigating the consequences of a lack of endogenous histamine in conditions of dopaminergic denervation. The genetic lack of histamine was found to be associated with altered post-lesion motor behavior as well as the upregulation of striatal markers of pre- and postsynaptic neurotransmitter function.

Post-lesion dopaminergic motor dysfunction was assessed by measurements of drug-induced rotation (motor imbalance) and LID. Amphetamine was found to induce more rotations in HDC KO mice when compared to wildtype mice. Such a genotype difference in rotation could indicate a difference in lesion extent [18]; however, no difference was found in TH-positive immunostaining remaining in the SNc. The present behavioral observation is in line with some previous

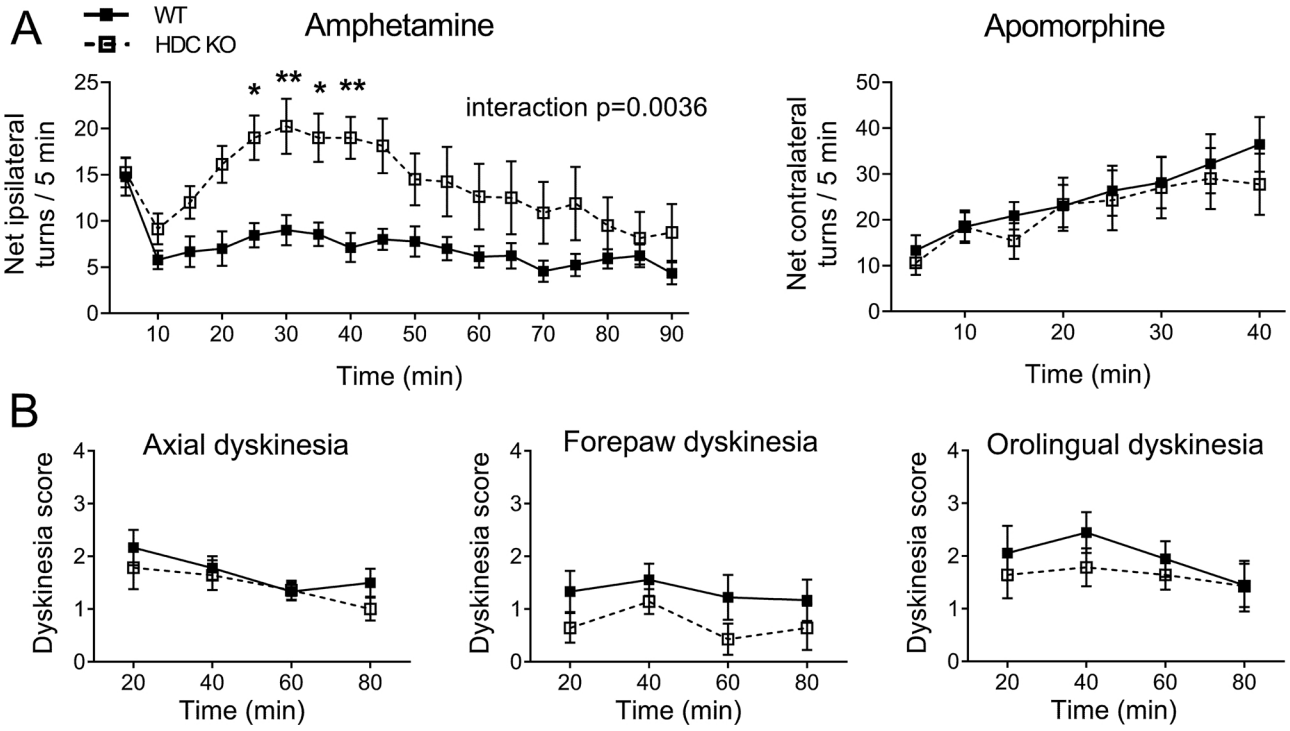

Fig. 2. Behavioral characterization of hemiparkinsonian HDC KO mice. A: Rotational behavior induced by amphetamine (2.5 mg/kg) and apomorphine (0.5 mg/kg) in mice with unilateral dopaminergic lesions. Amphetamine-induced rotations were increased in HDC KO mice, while there was no difference between genotypes in apomorphine-induced rotations. Mean rotations per 5 min ± SEM shown, $n_{WT} = 9$ $n_{KO} = 8$; 2-way RM ANOVA; *$p < 0.05$, **$p < 0.01$, Sidak's *post hoc* tests. **B**: Dyskinesia scores after two weeks of levodopa administration in mice with unilateral dopaminergic lesions. Dyskinesia severity did not differ between genotypes. Mean dyskinesia scores ± SEM shown, $n_{WT} = 9$ $n_{KO} = 7$.

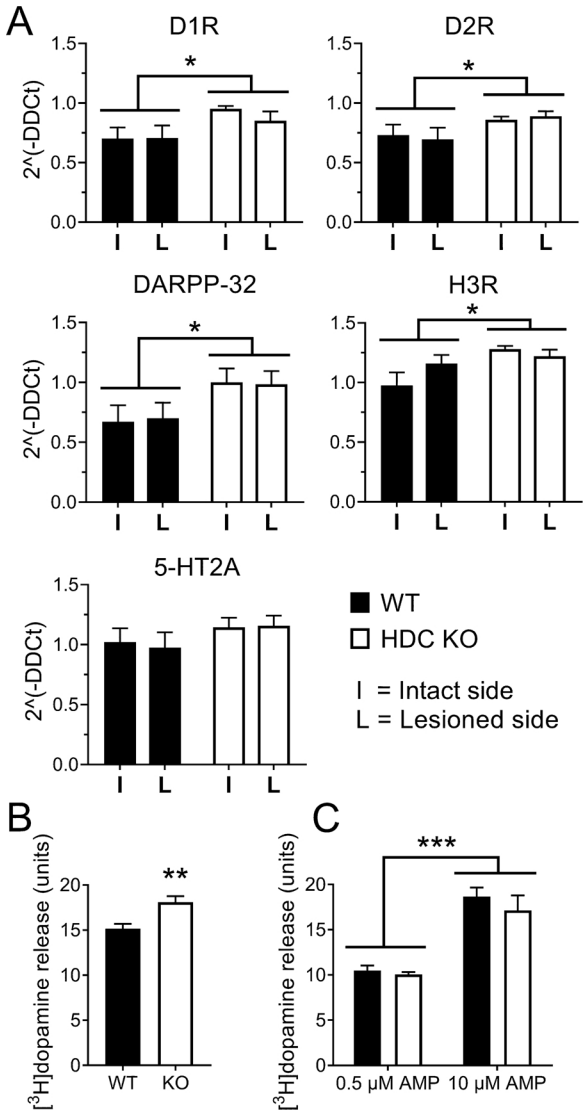

Fig. 3. Characterization of neurotransmitter function in HDC KO mice. A: Striatal mRNA levels of neurotransmitter biomarkers in the intact and lesioned hemispheres of mice with unilateral dopaminergic lesions. The expression of mRNA for D1R, D2R, DARPP-32 and H3R was increased in HDC KO mice. Mean of relative expression + SEM shown, n_{WT} = 8–9, n_{KO} = 8. **B–C**: Stimulated [^{3}H] dopamine release from striatal synaptosomes from unlesioned mice. Depolarization-stimulated [^{3}H]dopamine release (B) was significantly increased in HDC KO animals. However, the lack of histamine had no effect on half-maximal (0.5 µM) or maximal (10 µM) amphetamine (AMP)-induced [^{3}H] dopamine release (C). Mean stimulated release + SEM shown, n_{WT} = 5, n_{KO} = 6, four replicates per mouse. *p < 0.05, ***p < 0.001, 2-way RM ANOVA; **p < 0.01, *t*-test.

studies using unlesioned mice: methamphetamine has been reported to induce more locomotor activity in HDC KO than wildtype mice [19,20]. However, other studies have observed attenuated [21] or unchanged [22] amphetamine-induced motor activity in unlesioned HDC KO mice.

Previous literature thus, while conflicting, suggests that the presently observed genotype difference in amphetamine-induced motor behavior may not be exclusive to conditions of dopaminergic denervation. However, the alterations underlying this difference may be exacerbated in conditions of dopaminergic denervation, possibly explaining the contrasting findings in unlesioned mice in some studies, one of which [22] notably used the same mouse line as the present study. The specific nature of these alterations or how they are caused by the lack of histamine remains unclear, but elevated nigrostriatal dopaminergic function could play a role. This is suggested by the present findings of upregulation in markers of the dopaminergic system along with previous findings in HDC KO mice such as increased *in vivo* basal dopamine levels [23] and increased dopamine tissue concentrations after a methamphetamine challenge [19].

The lack of histamine had no effect on apomorphine-induced rotations. The effects of apomorphine have not to our knowledge been previously studied in mice completely lacking histamine. However, previous studies have found that drug-induced histamine depletion can attenuate apomorphine-induced rotations in 6−OHDA-lesioned rats [24,25]. It is possible that in the genetic model of histamine deficiency, compensatory mechanisms are masking differences in apomorphine-induced behavior that are revealed by pharmacologically induced histamine depletion.

Dyskinetic behaviors induced by repeated levodopa administration were, to our knowledge, here measured for the first time in mice lacking endogenous histamine. We hypothesized that LID would be altered in histamine-deficient mice on the basis of the abundant interactions between the histaminergic and dopaminergic systems [3], the LID-reducing effects of H2R and H3R ligands in animal models [8–11], and the ability of striatal histaminergic fibers to release levodopa-derived dopamine [26]. Surprisingly, dyskinesia did not differ between genotypes, despite evidence for postsynaptic dopaminergic upregulation in the same HDC KO mice. While the reason for this discrepancy is unknown, LID is also influenced by many neurotransmitter systems other than dopamine [2] that were not investigated here. Also note that different 6−OHDA models vary in their characteristics and potential applications [18]. It could be of interest to study LID also in histamine-lacking mice treated with intrastriatal 6−OHDA, a model where the extent and topography of dopaminergic neurodegeneration is markedly more restricted.

Significant upregulation of a number of biochemical dopaminergic markers was observed in the histamine-deficient mice. In lesioned HDC KO mice, qPCR assays revealed elevated striatal expression of D1R, D2R and DARPP-32 mRNA, suggesting the upregulation of postsynaptic dopaminergic function. This finding is in contrast with a previous study using unlesioned HDC KO mice, where no genotype differences were found in these markers using *in situ* hybridization [27]. As in the present study the mice were lesioned and administered dopaminergic drugs, the increased mRNA levels in histamine-deficient mice could reflect processes unique to the parkinsonian and levodopa-treated condition. mRNA levels were unchanged by the lesion itself, possibly due to reversal of any changes by the dopaminergic drug treatment [28].

In naïve HDC KO mice, depolarization-induced [^{3}H]dopamine release from striatal synaptosomes was increased, indicating presynaptic alterations resulting in increased dopamine release. This result is in line with previous studies on striatal dopamine and metabolite tissue concentrations suggesting increased dopamine turnover in HDC KO mice [22,29], as well as our own similar tissue concentration findings (unpublished). Note that due to the continuous superfusion histamine is not significantly present in the synaptosomal assay in either HDC KO or WT preparations. Considering this isolated nature of the synaptosomal preparation, the presynaptic alterations observed are likely to be long-term consequences of the lack of histamine. Interestingly, no genotype difference was observed in amphetamine-induced [^{3}H]dopamine release. The increased responsiveness to amphetamine observed in the HDC KO mice was thus unlikely to be mediated directly at the presynaptic sites of amphetamine's mechanisms of action.

Striatal H3R mRNA levels were increased in HDC KO mice, in line with a previous report [30]. Although H3R upregulation has been previously observed in Parkinson's disease patients [7] and in 6−OHDA-lesioned rats [31], we observed no statistically significant difference in H3R mRNA between the lesioned and intact hemispheres. Striatal expression of 5-HT2A receptor mRNA was unchanged by the lack of histamine or the dopaminergic lesion.

The present biochemical findings of increased release of dopamine

and increased expression of dopamine receptor and DARPP-32 mRNA suggest that the lack of brain histamine in HDC KO mice results in significant pre- and postsynaptic upregulation of striatal dopaminergic neurotransmission. Furthermore, the novel behavioral finding of increased hemiparkinsonian motor dysfunction in HDC KO mice could indicate that the alterations in dopaminergic activity are significant enough to be reflected in changes in motor behavior. While parkinsonism is characterized by a lack of striatal dopamine, enhanced dopaminergic function would not necessarily be beneficial, given the fundamental role of irregular dopamine release in e.g., LID. Taken together, our findings, along with the previous literature, suggest a complex histaminergic modulation of nigrostriatal dopaminergic neurotransmission in both healthy and parkinsonian conditions. This interplay may be significantly affected by dopaminergic denervation and can be altered, potentially disruptively, by a lack of histamine and thus quite possibly also other changes in the histaminergic system.

In conclusion, the study revealed important aspects on how the neuronal histaminergic system influences the dopaminergic system in the rodent brain, and represents new evidence for the complex interplay between the two neurotransmitter systems within the nigrostriatal pathway. Further studies, such as *in vivo* microdialysis experiments measuring dopamine directly in the striatum of intact and lesioned animals, could reveal in more detail how the lack of histamine alters striatal dopamine neurotransmission in the healthy and parkinsonian brain. Finally, the findings raise hope that further investigation of the histaminergic system in Parkinson's disease could shed new light on the mechanisms of the disease and suggest potential new treatments.

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CRediT authorship contribution statement

Sini K. Koski: Investigation, Formal analysis, Writing - original draft, Visualization. **Sakari Leino:** Investigation, Formal analysis, Writing - review & editing. **Pertti Panula:** Conceptualization, Methodology, Resources. **Saara Rannanpää:** Conceptualization, Investigation, Supervision. **Outi Salminen:** Conceptualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflict of interest.

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