

# Histaminergic control of corticostriatal synaptic plasticity during early postnatal development

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## Abstract

A reduction in the synthesis of the neuromodulator histamine has been associated with Tourette's syndrome and obsessive-compulsive disorder. Symptoms of these disorders are thought to arise from a dysfunction or aberrant development of corticostriatal circuits. Here, we investigated how histamine affects developing corticostriatal circuits, both acutely and longer-term, during the first postnatal weeks, using patch-clamp and field recordings in mouse brain slices (C57Bl/6, male and female). Immunohistochemistry for histamine-containing axons reveals striatal histaminergic innervation by the second postnatal week and qRT-PCR shows transcripts for H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub> histamine receptors in striatum from the first postnatal week onwards, with pronounced developmental increases in H<sub>3</sub> receptor expression. Whole-cell patch-clamp recordings of striatal spiny projection neurons and histamine superfusion demonstrates expression of functional histamine receptors from the first postnatal week onwards, with histamine having diverse effects on their electrical properties, including depolarization of the membrane potential whilst simultaneously decreasing action potential output. Striatal field recordings and electrical stimulation of corticostriatal afferents revealed that histamine, acting at H<sub>3</sub> receptors, negatively modulates corticostriatal synaptic transmission from the first postnatal week onwards. Lastly, we investigated effects of histamine on longer-term changes at developing corticostriatal synapses and show that histamine facilitates NMDA receptor-dependent long-term potentiation via H<sub>3</sub> receptors during the second postnatal week, but inhibits synaptic plasticity at later developmental stages. Together, these results show that histamine acutely modulates developing striatal neurons and synapses and controls longer-term changes in developing corticostriatal circuits, thus providing insight into the possible aetiology underlying neurodevelopmental disorders resulting from histamine dysregulation.

## Significance Statement

Monogenic causes of neurological disorders, although rare, can provide opportunities to both study and understand the brain. For example, a nonsense mutation in the coding gene for the histamine-synthesizing enzyme has been associated with Tourette's syndrome and obsessive-compulsive disorder, and dysfunction of corticostriatal circuits. Nevertheless, the aetiology of these neurodevelopmental disorders and histamine's role in the development of corticostriatal circuits has remained understudied. Here we show that histamine is an active neuromodulator during the earliest periods of postnatal life and acts at developing striatal neurons and synapses. Crucially, we show that histamine permits NMDA receptor-dependent corticostriatal synaptic plasticity during an early critical period of postnatal development, which suggests that genetic or environmental perturbations of histamine levels can impact striatal development.

## 94 Introduction

95 In the adult brain the neuromodulator histamine controls many processes, including  
96 sleep-wakefulness and levels of attention and vigilance, amongst others (Schwartz *et*  
97 *al.*, 1991; Haas & Panula, 2003; Panula & Nuutinen, 2013). The main neuronal  
98 sources of histamine are the histaminergic neurons located in the tuberomamillary  
99 nucleus (TMN) of the hypothalamus, which possess widespread axonal arborizations  
100 and release histamine throughout the brain (Inagaki *et al.*, 1988). Released histamine  
101 acts mainly at three distinct metabotropic histamine receptors expressed in the central  
102 nervous system: the H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub> receptors, which are each coupled to distinct  
103 intracellular pathways and regulate many cellular processes (Haas & Panula, 2003).  
104 Not only do the histaminergic neurons in the TMN start synthesizing histamine  
105 prenatally, the young developing brain also contains additional transient sources of  
106 histamine, such as raphe serotonergic neurons (Auvinen & Panula, 1988; Vanhala *et*  
107 *al.*, 1994), ependymal cells lining the ventricle, and mast cells (Nissinen & Panula,  
108 1995; Panula *et al.*, 2014) amongst others (Zecharia *et al.*, 2012), but the functional  
109 role for histamine during early brain development remains largely unknown.

110 A rare mutation in the gene coding for the histamine-synthesizing enzyme,  
111 *histidine decarboxylase*, which results in overall lower levels of histamine synthesis,  
112 was described in a group of patients diagnosed with Tourette's syndrome and  
113 obsessive-compulsive disorder (Ercan-Sencicek *et al.*, 2010). The symptoms seen in  
114 these disorders are thought to arise from dysfunction of the basal ganglia (Mink,  
115 2001; Albin, 2006; Yael *et al.*, 2015); an interconnected network of subcortical nuclei  
116 important in motor behavior and cognitive function (Graybiel *et al.*, 1994; Grillner *et*  
117 *al.*, 2005). The striatum is the main input nucleus of the basal ganglia, which exhibits  
118 extensive modulation by histamine in adulthood (Doreulee *et al.*, 2001; Ellender *et*  
119 *al.*, 2011; Castellan Baldan *et al.*, 2014; Bolam & Ellender, 2016; Rapanelli *et al.*,  
120 2017a), and much evidence points to alterations in cortico-striatal-thalamo-cortical  
121 loops in Tourette's syndrome (Felling & Singer, 2011; McNaught & Mink, 2011). A  
122 series of *in vivo* studies using mice with reduced brain histamine levels, either through  
123 gene knockout (Castellan Baldan *et al.*, 2014; Abdurakhmanova *et al.*, 2017) or  
124 acutely through chemogenetic manipulation of histaminergic neurons (Rapanelli *et*  
125 *al.*, 2017a; Rapanelli *et al.*, 2017b), have shown that this can recapitulate some key  
126 symptoms, e.g. increases in repetitive behaviors, as a result of changes in striatum.  
127 However, these studies were focused on adult animals, which limits our

understanding of histamine's role during early striatal development as well as in relation to neurodevelopmental disorders.

Here we explored whether histamine modulates the properties of the main neurons of the striatum: the GABAergic spiny projection neurons (SPNs) and their synaptic inputs during the earliest periods of postnatal life when SPNs are maturing and synapses are forming (Tepper *et al.*, 1998; Kozorovitskiy *et al.*, 2012; Peixoto *et al.*, 2016; Krajewski *et al.*, 2019; Peixoto *et al.*, 2019). Experiments were performed during the first postnatal week (i.e. postnatal day 3-6) when most striatal SPNs have been born but excitatory synaptic inputs are thought to be minimal, the second postnatal week (i.e. postnatal 9-12) when excitatory inputs are undergoing a period of rapid maturation, and young adulthood (i.e. postnatal day 21-35) when the striatal SPNs and circuits are thought to be approaching maturity (Tepper *et al.*, 1998; Khazipov *et al.*, 2004; Dehorter *et al.*, 2011; Kozorovitskiy *et al.*, 2012; Peixoto *et al.*, 2016; Peixoto *et al.*, 2019) with mice reaching sexually maturity at 35 days (Foster *et al.*, 1983). We find that histamine widely modulates both the electrical properties of striatal neurons as well as the developing corticostriatal synapses, during the earliest periods of postnatal life. Importantly, we find that histamine has a key role in permitting longer-term synaptic changes at corticostriatal synapses during an early critical period of development. Overall, these results suggest that altered histamine levels, as a result of genetic mutations or environmental factors, could acutely, can affect developing corticostriatal circuits.

## Materials and Methods

### Animals

All experiments were carried out on C57Bl/6 wildtype mice of both sexes with *ad libitum* access to food and water. Experiments were designed to use litter mates for the various developmental age ranges within single experiments to control for effects of litter sizes and maternal care factors that could affect degree of neuronal and circuit maturity. All mice were bred and IVC housed in a temperature controlled animal facility (normal 12:12 h light/dark cycles) and used in accordance with the UK Animals (Scientific Procedures) Act (1986).

### Slice preparation and recording conditions

Acute striatal slices were made from postnatal animals between postnatal day (P)3-6, P9-12 or P21-35. A small number of mice older than P35 were used for a subset of additional experiments and results obtained have been reported where appropriate. The mice were anaesthetized with isoflurane and then decapitated. Coronal 350-400  $\mu\text{m}$  slices were cut using a vibrating microtome (Microm HM650V). Slices were prepared in artificial cerebrospinal fluid (aCSF) containing (in mM): 65 Sucrose, 85 NaCl, 2.5 KCl, 1.25  $\text{NaH}_2\text{PO}_4$ , 7  $\text{MgCl}_2$ , 0.5  $\text{CaCl}_2$ , 25  $\text{NaHCO}_3$  and 10 glucose, pH 7.2-7.4, bubbled with carbogen gas (95%  $\text{O}_2$  / 5%  $\text{CO}_2$ ). Slices were immediately transferred to a storage chamber containing aCSF (in mM): 130 NaCl, 3.5 KCl, 1.2  $\text{NaH}_2\text{PO}_4$ , 2  $\text{MgCl}_2$ , 2  $\text{CaCl}_2$ , 24  $\text{NaHCO}_3$  and 10 glucose, pH 7.2-7.4, at 32 °C and bubbled with carbogen gas until used for recording. Field recordings were performed in striatal slices transferred to an interface chamber (Scientific Systems Design, Hofheim, Germany) and continuously superfused with aCSF bubbled with carbogen gas with the same composition as the storage solution (32 °C and perfusion speed of 2 ml/min). Recordings were made using glass pipettes, pulled from standard wall borosilicate glass capillaries and containing aCSF using a Multiclamp 700A amplifier (Axon Instruments, Molecular Devices, CA, USA), filtered at 4 kHz and acquired at 10 kHz using a X-series USB-6341 A/D board (National Instruments, Texas, USA) and WinWCP software (University of Strathclyde, RRID:SCR\_014713). Recordings from single neurons were made in striatal slices in a submerged recording chamber (Slicescope Pro 1000, Scientifica, UK) continuously superfused with aCSF bubbled with carbogen gas with the same composition as the storage solution (32 °C and

perfusion speed of 2 ml/min). Whole-cell current-clamp recordings were performed using glass pipettes, pulled from standard wall borosilicate glass capillaries (to minimise dialysis of cytosolic components we used 6-8 M $\Omega$  resistance pipettes), and containing for whole-cell current-clamp (in mM): 110 potassium gluconate, 40 HEPES, 2 ATP-Mg, 0.3 Na-GTP, 4 NaCl and 4 mg/ml biocytin (pH 7.2-7.3; osmolarity, 290-300 mosmol/l). Recordings were made using a Multiclamp 700B amplifier and filtered at 4kHz and acquired at 10 kHz using an InstruTECH ITC-18 analog/digital board and WinWCP software (University of Strathclyde, RRID:SCR\_014713) at 10 kHz.

#### Stimulation and recording protocols field recordings

Activation of excitatory cortical afferents was performed using a bipolar stimulating electrode (FHC Inc., USA) or a glass electrode placed in the deep layers of the cortex at a distance to the striatum to avoid direct activation of striatal neurons. Electrical stimulating pulses were given using a DS2 Isolated Stimulator (Digitimer, UK) ranging from 10 to 100 V and 200  $\mu$ s in duration and stimulation strength was chosen to give half-maximum field excitatory postsynaptic potentials (fEPSPs) as recorded from a glass electrode placed in dorsal striatum. All recordings were made in the presence of the GABA<sub>A</sub>-receptor antagonist SR95531 (gabazine; 200 nM). The stability of fEPSPs during recordings was assessed for 20-30 minutes prior to start of experiments and only recording conditions where the fEPSP amplitude changed less than 10% were accepted. Cortical afferents were activated every 5-10s in both drug superfusion and synaptic plasticity experiments. Trains of stimulations consisted of 6 pulses given at 20 Hz repeated at 30 s intervals up to 5 times. Long-term synaptic plasticity protocols consisted of stimulation of cortical afferents at 5-10 s intervals for a minimum of 5 minutes to obtain a stable baseline measurement of fEPSP amplitude, after which afferents were transiently stimulated using a theta-burst stimulation (TBS) paradigm consisting of brief bursts of stimulation at either 10Hz or 50Hz. These bursts consisted of 13 pulses given at 10Hz or 50Hz and were repeated 20 times with a 200 ms interval. After this protocol, afferents were activated every 5-10 s for at least 40 minutes to assess potential longer-term changes in fEPSP amplitude.

### Stimulation and recording protocols single neuron recordings

Hyperpolarizing and depolarizing current steps were used to assess the intrinsic properties of recorded SPNs in dorsal striatum including input resistance and spike threshold (using small incremental current steps) as well as the properties of action potentials (amplitude, frequency and duration). Currents step ranges for P3-6 slices were: -50pA to +50pA, for P9-12: -100pA to +100pA and for P21-35: -500pA to +500pA. These ranges of currents were chosen to allow sufficient depolarization of SPNs, taking in consideration changes in input resistance and observations of depolarization block and action potential failure in SPNs. A distinction between striatal SPNs and interneurons was made based on our previous experience (Ellender *et al.*, 2011; Krajeski *et al.*, 2019) and involved a combined assessment of resting membrane potential, input resistance, delay to firing and overall action potential frequency, and if in doubt neurons were excluded from experiments and/or data analysis. The stability of whole-cell recordings was assessed for 1-3 minutes prior to the start of experiments, including measurements of input resistance and holding current and if these changed during this period by more than 10% the neuron was discarded.

### Analysis of recordings

Data were analyzed offline using custom written programmes in Igor Pro (Wavemetrics, RRID:SCR\_000325). The input resistance was calculated from the observed membrane potential change after hyperpolarizing the membrane potential with a set current injection. The membrane time constant was calculated as the time it took to reach 63% of the final membrane potential change after hyperpolarizing the membrane potential. The resting membrane potential was obtained continuously during recordings and the first 5 minutes of recordings in aCSF were compared to the last 5 minutes of recordings in the presence of histamine. Individual recording sweeps exhibiting large noise fluctuations were manually removed from analysis. The rheobase was the minimal current injection needed for a striatal SPN to generate an action potential. Time to 1<sup>st</sup> spike was the time between the start of the depolarizing step and the emergence of the first observed action potential. The spike rate was calculated from the total number of action potentials observed at the indicated depolarizing step. Other intrinsic properties were calculated from cellular responses after depolarizing steps for P3-6 at +40pA, for P9-12 at +90pA and for P21-35 at

+400pA. The ISI (or Interspike Interval) was the time between two subsequent action potentials with the 1<sup>st</sup> ISI referring to the time between the first and second action potential. The action potential amplitude was taken from the peak amplitude of the individual action potential relative to the average steady-state membrane depolarization during positive current injection. Action potential duration was taken as the duration between the upward and downward stroke of the action potential at 25% of the peak amplitude. Field (f)EPSP properties were analysed from average fEPSPs derived from at least 20 sweeps. fEPSP recordings often included a clear stimulation artefact followed by a first negativity (so called N1) which reflects direct activation of neurons and axons presynaptic fiber volley and a second negativity (so called N2) which reflect synaptic transmission (Malenka & Kocsis, 1988; Flagmeyer *et al.*, 1997) and the later was used for fEPSP measurements. Measurements include peak amplitude (measured as the difference between the pre-stimulus voltage and the peak of the fEPSP), duration (measured from the start of the upward/downward stroke of the event until its return to the pre-event baseline), rise time (time between 20% and 80% of the peak amplitude) and decay time (measured as the time from peak amplitude until the event returned to baseline). The short-term plasticity at cortical afferents was derived from the amplitude of each fEPSP during train stimulation divided by the amplitude of the first response.

### Histological analyses

Histaminergic afferents were revealed in fixed brain sections using a modification of a previously described protocol (Ellender *et al.*, 2011). In brief, P3-6, P9-12 or P21-35 old C57Bl/6 mice were anaesthetized with isoflurane and brains removed and washed in ice-cold cutting aCSF and immediately transferred to ice-cold 4% 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide HCl (EDC, Thermo Fisher Scientific, Cat. 22981) in 0.1 M PB, pH 6.0 and kept at 4°C for 3 days followed by further fixation in 4% paraformaldehyde in 0.1 M PBS for 2 days. Sagittal and coronal vibratome sections (40 µm) were collected and subjected to antigen retrieval by heating at 80°C in 10 mM sodium citrate (pH 6.0) for 20-30 min. Sections were then blocked with 10% normal goat serum (Jackson Immuno Research, AB\_2336990 Cat. 005-000-121, Lot. 142539) in PBS containing 1% Triton X-100 (PBS-Tx) for 1 h, at room temperature, followed by incubation for 4 days with 1:500 anti-rabbit histamine antibody (Immunostar, AB\_572245, Cat. #22939, Lot: 1532001) in PBS at 4°C under



gentle agitation. After this, sections were washed and incubated in 1:500 biotinylated goat-anti-rabbit IgG (Invitrogen, Cat.B2770, Lot.1870403) overnight at 4°C. The sections were then washed and incubated in Vectastain ABC Elite (Vector Laboratories, AB\_2336827, Cat. PK-6100, Lot. ZF0425) for 4 hours at room temperature under gentle agitation, followed by incubation with 1:1000 DAPI for 10 min. Sections were washed thoroughly and then incubated overnight at 4°C in 1:1500 ZyMax anti-streptavidin-Cy3 fluorophore (Invitrogen, Cat.438315, Lot.1001066A). Finally, all sections were mounted in Vectashield (Vector Laboratories, Cat. H-1000, Lot. ZF0409) and images were captured with a Leica DM5000B epifluorescence microscope using Openlab software (PerkinElmer Life and Analytical Sciences). Images were processed in Adobe Photoshop CS3 and Adobe Illustrator CS3. Measurements of histamine axonal length and intensity were performed using single representative images consisting of 1mm<sup>2</sup> regions of cortex and dorsal striatum containing histamine axons using ImageJ software. Axonal fluorescence signal was measured as the difference in signal between background (average of 30+ points outside of axonal fibers) and the signal within axonal fibers (average of 30+ points inside of axonal fibers) and is expressed as % above background. Axons were detected manually in images but the fluorescent signal within axons had to pass a threshold of 2 standard deviations above the background signal. Total axonal length was derived from manually traced axons within the 1mm<sup>2</sup> regions. Axonal arborizations were manually counted during tracing of axons.

#### Quantitative RT-PCR

Acute brain slices (400 µm) from P3-6, P9-12 or P21-35 C57Bl/6 mice were made as previously described with the addition of thorough cleaning of all tools and the vibratome with RNaseZAP (Sigma, Cat. R2020) and wiping the surfaces using RNase Decontamination Wipes (Thermo Fisher Scientific, Cat. AM9786). Brain slices containing the striatum were collected with a brush and transferred into a 1.5 ml RNase-free tube containing 700-1000 µl of RNAlater (Invitrogen, Cat. AM7020) and incubated at 4°C for at least 24 hours. After incubation, the brain slices were removed from RNAlater solution and transferred to a Petri dish pre-treated with RNase ZAP and containing sterile cutting aCSF. The striatum was dissected under a light microscope, and the sections of striatum were collected in a QIAshredder column (QIAGEN, Cat. 7905A) containing 300 µl of PureLink lysis buffer solution

320 (Invitrogen, Cat. 12183018A). The striatal tissue was centrifuged at 20,000xg  
 321 (Eppendorf Centrifuge, model 5424) to disrupt the tissue. After this, one volume of  
 322 70% ethanol was added to the homogenate and vortexed to disperse any precipitate.  
 323 The full volume was transferred to a PureLink spin cartridge and centrifuged (15 s,  
 324 13,000xg). Further washing steps were carried on according to the PureLink  
 325 manufacturers' instructions. Elution of mRNA was performed with 50 µl of the  
 326 manufacture-provided Elution Buffer. mRNA quantity and quality were assessed  
 327 using a Nanodrop spectrophotometer (ND-1000) and a 1% agarose gel was used to  
 328 confirm mRNA quality. A cDNA library was generated from 1 µg of striatal mRNA  
 329 using the Super Script IV VILO kit (ThermoFisher, Cat. 11766050). The genomic  
 330 DNA digestion, RT and no-RT reactions were prepared according to the  
 331 manufacturer's instructions. cDNA samples were kept at -80°C until needed. For the  
 332 quantitative RT-PCR, three pairs of primers targeting the exon-intron region of the  
 333 histamine H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub> receptor transcripts as well as the β-actin transcript, were  
 334 designed using the NCBI primer blast web server  
 335 (<https://www.ncbi.nlm.nih.gov/tools/primer-blast/>) and verified using the oligo  
 336 analyzer Beacon Designer (PRIMER Biosoft International), and were initially tested  
 337 for amplification cycle and specificity, and a single pair was used for all future  
 338 experiments. Primers used for quantitative RT-PCR experiments include for H<sub>1</sub> (*Fwd*:  
 339 TGACCAGACCTTGAGCCAGCCCAAAATG and *Rev*:  
 340 AGACCTGCTTCTCGCTTTGACTTTGCCC), H<sub>2</sub> (*Fwd*:  
 341 CCACAACCTCTCACAAAACCTTCC and *Rev*: CTTCTCCTCCTGCCATCTAC), H<sub>3</sub>  
 342 (*Fwd*: TGCACAGGTATGGGGTGGGTGAG and *Rev*:  
 343 CCAAGGACGCTGAAGACGCTGATG), H<sub>4</sub> (*Fwd*:  
 344 TGGAAGAACAGCACGAACACAAAGGAC and *Rev*:  
 345 GAAATAAGCCACAGAGATGACAGGAAGCAG) and β-actin (*Fwd*:  
 346 CCAGCCTTCCTTCTTGGGTATC and *Rev*:  
 347 CTTTACGGATGTCAACGTCACAC). The primers were resuspended according to  
 348 the manufacturer instructions to a concentration of 100 µM. A primer aliquote was  
 349 used to obtain a 2 µM stock solution. A mix was prepared for each reaction,  
 350 containing 5 µl of PowerUp SYBER Green Master Mix (ThermoFisher, Cat.  
 351 100029284), 1 µl of the forward primer, 1 µl of the reverse primer (final  
 352 concentration of 200 nM each primer, 1:10 dilution from the 2 µM stock solution) and

1  $\mu$ l of nuclease free water. 2  $\mu$ l of the cDNA (~1 ng) of each striatal age group (P3-6,  
P9-12 or P21-35) was added to the corresponding wells in a 96-well plate, for a final  
volume of 10  $\mu$ l per reaction.  $\beta$ -actin was used as housekeeping gene, and samples  
were prepared following the same procedure. After this, the 96-well plate was  
covered with a Microseal 'B' seal (BIO-RAD Cat. MSB1001) and centrifuged  
(1000xg, 10 s). The quantitative RT-PCR was performed following the PowerUp  
SYBER Green manufacturer's instructions and results were detected with a CFX96  
real-time PCR detection system (Bio-Rad, Cat. 184-5384). Data was collected from  
the striatal mRNA of three mice per age group (three biological replicates). Each  
experiment was designed to test for H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub> receptor mRNA expression in  
the same age group, with each receptor being measured by triplicate (technical  
replicates). Data analysis was performed using the  $\Delta$ Ct method, and normalized  
against the respective  $\beta$ -actin control samples. A 0.05  $\Delta$ Ct<sup>-1</sup> cut-off was set, which  
corresponds to the minimum  $\Delta$ Ct value within a window comprising the  $\beta$ -actin Ct  
values and the maximum 40x Ct amplification cycles. In addition, a threshold of 100  
RFU was set for accepting an amplification curve.

#### Experimental Design and Statistical Analysis

All data are presented as means  $\pm$  SEM. The 'n' refers to the number of neurons,  
brain sections, RT-PCR samples / the number of C57Bl/6 wildtype mice of both sexes  
tested. Statistical tests were all two-tailed and performed using SPSS 17.0 (IBM SPSS  
statistics, RRID:SCR\_002865) or GraphPad Prism version 5.0 (GraphPad software,  
RRID:SCR\_002798). Continuous data were assessed for normality and appropriate  
parametric (ANOVA, paired *t*-test and independent *t*-test) or non-parametric (Mann-  
Whitney U, Wilcoxon Signed Rank and Kruskal-Wallis) statistical tests were applied  
(\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ).

#### Drugs and chemicals

Drugs used in electrophysiological experiments included histamine (10  $\mu$ M), the H<sub>3</sub>  
receptor antagonist thioperamide (10  $\mu$ M), the NMDA receptor antagonist D-AP5 (50  
 $\mu$ M) and the GABA<sub>A</sub> receptor antagonist SR95531 (200 nM). A concentration-  
response pilot experiment for histamine (range of 1-100  $\mu$ M) reducing the amplitude  
of electrically evoked corticostriatal EPSPs gave an IC<sub>50</sub> of 1.2  $\mu$ M with a maximum

386 effect at 5  $\mu$ M (Ellender *et al.*, 2011). All drugs were obtained from Tocris  
387 Biosciences (Bristol, UK).

388

## Results

### The striatum contains histaminergic afferents from the second postnatal week onwards

The early postnatal mouse brain contains several sources of histamine, with the main neuronal source being the histaminergic neurons of the TMN, which start producing histamine prenatally and continue to do so throughout postnatal life (Auvinen & Panula, 1988; Vanhala *et al.*, 1994; Nissinen & Panula, 1995). In adulthood it has been shown that histaminergic neurons of the TMN innervate extensive regions of the brain including the striatum (Haas & Panula, 2003). Here we explored whether histaminergic afferents are present in the cortex as well as the striatum of younger C57Bl/6 mice at postnatal day 3-6, P9-12 and P21-35 (n = 3 mice for each age range, **Fig. 1A**). A polyclonal antibody against histamine was used to label histamine-containing structures in 40 µm thick sections of 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide HCl (EDC)-fixed brains and produced clear labeling of histaminergic neurons in the TMN (**Fig. 1B**). In P3-6 mice histaminergic afferents were detected in the cortex (fluorescence signal expressed as % above background:  $56.18 \pm 14.32\%$ ) but not in the striatum (**Fig. 1C and F**). In contrast, histamine immunoreactivity could be readily seen in both cortex and striatum at P9-12 (cortex  $69.76 \pm 30.15\%$  and striatum:  $89.56 \pm 30.95\%$ ) and consisted of thin axonal structures with minimal arborization (cortex, axonal length:  $102.01 \pm 9.16\mu\text{m}$ , no arborization and striatum, axonal length:  $67.68 \pm 15.95\mu\text{m}$ , arborization:  $0.33 \pm 0.33$ , **Fig. 1D and F**). In P21-35 mice histamine-containing fibers were observed in both striatum and the cortex at higher densities and was significantly increased for striatum (cortex, axonal length:  $126.02 \pm 18.08\mu\text{m}$ , arborization:  $0.66 \pm 0.33$  and striatum, axonal length:  $111.3 \pm 6.88\mu\text{m}$ , arborization:  $3.33 \pm 0.33$ , axonal length striatum P9-12 vs P21-35  $F(2,6)=31.28$   $p=0.049$ , arborization striatum P9-12 vs P21-35  $F(2,6)=45.50$   $p=0.0006$ , ANOVA, n=3 mice **Fig. 1E and F**). These results suggest that histaminergic fibers in the cortex are present just after birth and that by P9-12 both cortex and striatum contain histaminergic axonal structures.

### Changes in relative expression levels of histamine receptor transcripts in the striatum

We next investigated to what extent histamine receptors are expressed in the striatum and whether expression levels change dynamically across postnatal development. The striatum was dissected from acute brain slices at the three developmental periods, followed by extraction of striatal mRNA and quantitative RT-PCR to assess transcript levels for the H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub> histamine receptors (**Fig. 2A** and **B**). Products of the quantitative RT-PCR produced clear single bands of predicted sizes (**Fig. 2C**). Transcript levels were compared to the housekeeping gene  $\beta$ -actin, which exhibited minimal change across postnatal development (Ct values at P3-6:  $17.59 \pm 0.10$ , P9-12:  $17.90 \pm 0.20$  and P21-35:  $18.40 \pm 0.34$ ,  $p=0.14$ , Kruskal-Wallis,  $n=12/3$  mice in each age group, **Fig. 2C** and **D**).

We found that transcripts for the H<sub>1</sub> receptor ( $\Delta Ct^{-1}$  values, P3-6:  $0.10 \pm 0.02$ , P9-12:  $0.12 \pm 0.01$  and P21-35:  $0.11 \pm 0.01$ ,  $n=3$  mice in each age group,  $F(2,6)=1.19$   $p=0.36$ , all vs P3-6 group, One-way ANOVA), and transcripts for the H<sub>2</sub> receptor remained predominantly constant throughout the developmental periods studied, with only a slight but significant increase for the H<sub>2</sub> receptor from P3-6 to P21-35 ( $\Delta Ct^{-1}$  values, P3-6:  $0.09 \pm 0.003$ , P9-12:  $0.10 \pm 0.002$  and P21-35:  $0.11 \pm 0.005$ ,  $F(2,6)=9.33$   $p=0.009$ , P3-6 vs P21-35,  $n=3$  mice in each age group, One-way ANOVA). In contrast, transcripts for the H<sub>3</sub> histamine receptor showed a rapid and significant increase from the first to the second postnatal week, and a further increase from the second postnatal week onwards ( $\Delta Ct^{-1}$  values, P3-6:  $0.10 \pm 0.02$ , P9-12:  $0.22 \pm 0.02$ , P21-35:  $0.25 \pm 0.02$ ,  $F(2,6)=21.89$ , P3-6 vs P9-12  $p=0.004$  and P3-6 vs P21-35  $p=0.0015$ , One-way ANOVA,  $n=3$  mice in each age group, **Fig. 2D**). We did not detect significant expression levels for the H<sub>4</sub> receptor at any of the developmental periods ( $\Delta Ct^{-1}$  values, P3-6:  $0.03 \pm 0.02$ , P9-12:  $0.01 \pm 0.03$ , P21-35:  $0.02 \pm 0.03$ , all vs P3-6 group,  $F(2,6)=0.99$   $p=0.42$ , One-way ANOVA  $n=3$  mice in each age group), suggesting that these receptors are not expressed in the striatum (Schneider & Seifert, 2016). In addition, we did not observe amplification in the no-RT reactions for either histamine receptors or  $\beta$ -actin (**Fig. 2B**). Together, these results suggest that the striatum already contains transcripts coding for the various histamine receptors from the first postnatal days onwards, and secondly, that expression levels are dynamic throughout development as exemplified by significant increases in transcript levels for the H<sub>2</sub> and H<sub>3</sub> histamine receptors.

## Histamine modulates the electrical properties of developing striatal spiny projection neurons

The observation that the striatum during the first postnatal weeks contains both histaminergic afferents and transcripts coding for the main histamine receptors, suggests that released histamine has the potential to act on developing striatal neurons and synapses. Therefore, we next investigated whether the intrinsic electrical properties of striatal spiny projection neurons (SPNs) was modulated by histamine by performing whole-cell patch-clamp recordings of SPNs at P3-6, P9-12 and P21-35 in combination with superfusion of histamine (5  $\mu$ M). The concentration of histamine was chosen based on previous experimental data (Ellender *et al.* 2011 and see Methods) and in accordance with previous studies (Jafri *et al.*, 1997; Brown & Haas, 1999; Atzori *et al.*, 2000; Doreulee *et al.*, 2001; Yu *et al.*, 2009; Ellender *et al.*, 2011; Zhuang *et al.*, 2018), reporting a concentration-response and IC<sub>50</sub>/EC<sub>50</sub> values of ~2-3  $\mu$ M with maximum effects seen at ~5  $\mu$ M. A combination of criteria was used to verify that recordings were made from SPNs (see Methods) and likely consisted of both D1 and D2 SPNs. Potential changes in the electrical properties of SPNs were measured by comparing the first 5 minutes in aCSF with the last 5 minutes after superfusion of histamine (5  $\mu$ M). Histamine modulated the intrinsic electrical properties of SPNs in complex ways from the earliest postnatal days onwards; at P3-6, superfusion of histamine mainly led to a significant decrease in the input resistance (aCSF:  $992.41 \pm 65.94\text{M}\Omega$  and histamine:  $647.68 \pm 72.79\text{M}\Omega$ ,  $p=0.0002$ , paired  $t$ -test,  $n=13/5$  mice, **Table 1** and **Fig. 3A**), and a hyperpolarization of the resting membrane potential (aCSF:  $-70.44 \pm 0.08\text{mV}$  and histamine  $-74.47 \pm 0.08\text{mV}$ ,  $p=0.0001$ , paired  $t$ -test, **Fig. 3A**). Despite these changes histamine did not significantly modulate the frequency of action potentials elicited by injecting increasing amounts of positive current (at +40pA, aCSF:  $14.58 \pm 1.78\text{Hz}$  and histamine:  $11.09 \pm 2.21\text{Hz}$ ,  $F(1,56)=1.28$   $p=0.26$ , Two-way ANOVA, **Fig. 3A**). In contrast, in the second postnatal week at P9-12 as well as during later developmental periods, histamine superfusion did not alter the input resistance of the SPNs (P9-12, aCSF:  $397.1 \pm 23.34\text{M}\Omega$  and histamine:  $345.7 \pm 25.35\text{M}\Omega$ ,  $p=0.06$ , paired  $t$ -test,  $n=22/7$  mice and P21-35, aCSF:  $113.4 \pm 10.62\text{M}\Omega$  and histamine:  $109.4 \pm 10.16\text{M}\Omega$ ,  $p=0.64$ , paired  $t$ -test,  $n=14/8$  mice, **Fig. 3B** and **C**) and during these periods histamine

superfusion now led to a significant depolarization of SPNs (P9-12, aCSF:  $-71.61 \pm 0.14$  mV and histamine:  $-67.50 \pm 0.06$  mV,  $p=0.0001$ , paired  $t$ -test,  $n=22/7$  mice and P21-35, aCSF:  $-70.99 \pm 0.21$  mV and histamine:  $-65.96 \pm 0.15$  mV,  $p=0.0001$ , paired  $t$ -test,  $n=14/8$  mice, **Fig. 3C and D**). Notwithstanding the observed depolarization of SPNs, the frequency of action potentials elicited by injecting increasing amounts of positive current was reduced at both P9-12 (aCSF:  $13.14 \pm 4.05$  Hz and histamine:  $9.07 \pm 2.99$  Hz,  $F(1,158)=20.09$   $p=0.0001$ , Two-way ANOVA, **Fig. 3C**) and P21-35 (aCSF:  $32.2 \pm 5.6$  Hz and histamine:  $26.5 \pm 3.82$  Hz,  $F(1,110)=9.99$   $p=0.002$ , Two-way ANOVA, **Fig. 3D**). The reduction in action potential frequency was concurrent with an overall increase in the duration of the interspike intervals, which was particularly prominent at P9-12 (% increase vs aCSF, P3-6:  $+10.09 \pm 0.15\%$ ,  $p=0.15$ , P9-12:  $+41.97 \pm 18.46\%$ ,  $p=0.02$  and P21-35:  $+8.71 \pm 2.01\%$ ,  $p=0.59$ , paired  $t$ -test, **Table 1**). Lastly, histamine modulated the membrane time constant of developing striatal SPNs and led to a shortening in the duration of the membrane time constant at P3-6 (aCSF:  $36.32 \pm 1.56$  ms and histamine:  $23.90 \pm 2.79$  ms,  $p=0.0029$ , paired  $t$ -test,  $n=12/5$  mice) and a minor prolongation at P21-35 (aCSF:  $2.67 \pm 0.16$  ms and histamine:  $3.49 \pm 0.37$  ms,  $p=0.008$ , paired  $t$ -test,  $n=16/8$  mice, **Table 1**). We did not find other histamine-mediated changes in the intrinsic electrical properties of striatal spiny projection neurons (**Table 1**).

Together, these data show that histamine can modulate the intrinsic electrical properties of developing striatal SPNs from the first postnatal days onwards. Overall, the main effect of histamine appears to be to change the membrane potential of SPNs in conjunction with a general reduction in their action potential output.

### **Histamine modulates excitatory glutamatergic transmission at developing corticostriatal synapses**

We next considered whether histamine was able to modulate the excitatory synaptic inputs to the developing striatum. Previously, it was shown that histamine could negatively modulate synaptic transmission by acting at presynaptic H<sub>3</sub> histamine receptors in adult mice (Doreulee *et al.*, 2001; Ellender *et al.*, 2011), but whether histamine modulates synaptic transmission at developing synapses also is unknown. We investigated the effect of histamine on transmission at developing corticostriatal synapses in acute brain slices kept in an interface chamber (Haas *et al.*, 1979), at the



interface between aCSF and humidified carbogen gas, and corticostriatal afferents  
 were activated using a stimulating electrode placed in the cortex (bordering the  
 external capsule) with field excitatory postsynaptic potentials (fEPSPs) recorded with  
 a glass electrode placed in dorsal striatum (**Fig. 4A**). This recording configuration  
 does not disturb the cytosolic components of SPNs (Lahiri & Bevan, 2020), as  
 synaptic events are recorded extracellularly, and allows for stable and long duration  
 recordings. Recorded fEPSPs are a reflection of the summed synaptic activity  
 occurring at a large numbers of corticostriatal excitatory synapses, principally on  
 striatal SPNs with a likely similar contribution of both D1 and D2 SPNs (Malenka &  
 Kocsis, 1988; Flagmeyer *et al.*, 1997). All recordings were performed in the presence  
 of the GABA<sub>A</sub> receptor antagonist SR95531 (gabazine; 200 nM) to minimize  
 recruitment of GABAergic afferents and facilitate isolation of glutamatergic afferents.  
 Indeed, evoked fEPSPs could be blocked by the addition of the glutamatergic  
 antagonists NBQX (40  $\mu$ M) and D-AP5 (50  $\mu$ M) to the aCSF (to  $9.24 \pm 8.76\%$  of  
 baseline amplitude,  $n = 5/3$  mice, **Fig. 4A**). In these experiments a slightly higher  
 concentration of histamine was used (10  $\mu$ M) to guarantee a sufficient concentration  
 of histamine under these recording conditions, with aCSF predominantly flowing  
 underneath slices, as has also been used extensively in previous studies (Jafri *et al.*,  
 1997; Brown & Haas, 1999; Atzori *et al.*, 2000; Doreulee *et al.*, 2001; Yu *et al.*, 2009;  
 Ellender *et al.*, 2011; Zhuang *et al.*, 2018). Three main observations were made  
 during these experiments. Firstly, we found that the properties of corticostriatal  
 fEPSPs were dynamic and changed during early postnatal development, similar to  
 previous observations made from single SPNs (Krajeski *et al.*, 2019), and include a  
 progressive increase in amplitude and a reduction in the duration of evoked fEPSPs  
 (**Table 2**). Secondly, we found that histamine (10  $\mu$ M) superfusion rapidly decreased  
 the amplitude of corticostriatal fEPSPs in all developmental periods (normalized  
 change in fEPSP amplitude, P3-6: to  $87.95 \pm 4.57\%$ , P9-12: to  $83.87 \pm 5.46\%$  and  
 P21-35: to  $83.29 \pm 4.04\%$ :  $p=0.046$ ,  $p=0.042$  and  $p=0.009$  respectively, paired *t*-test,  
 $n=6/5$  mice,  $5/5$  mice and  $6/6$  mice, **Fig. 4B-D**), and continued to do so in brain slices  
 from older animals also (P35+: to  $76.66 \pm 7.76\%$ ,  $p=0.008$ ,  $n=10/5$  mice). Other  
 properties of the fEPSPs were found to be unaffected by histamine superfusion  
 (**Table 3**). Such reductions in fEPSP amplitude were not observed during control  
 experiments consisting of continued superfusion with aCSF (normalized change in  
 fEPSP amplitude, P3-6: to  $100.82 \pm 2.22\%$ , P9-12: to  $100.38 \pm 1.48\%$  and P21-35: to

103.93  $\pm$  1.60%:  $p=1.000$ ,  $p=0.715$  and  $p=0.109$ , Wilcoxon Signed Rank Test,  $n=4/4$  mice,  $n=4/3$  mice and  $n=3/3$  mice, **Fig. 4B-D**). Lastly, to investigate at which receptors histamine might be acting we superfused histamine together with the H<sub>3</sub> receptor antagonist thioperamide, as histamine had previously been shown to regulate corticostriatal transmission through H<sub>3</sub> histamine receptors in adult mice (Doreulee *et al.*, 2001; Ellender *et al.*, 2011). The potent and selective H<sub>3</sub> receptor antagonist thioperamide acts in the nM range in cell-based assays (Arrang *et al.*, 1987; Hew *et al.*, 1990; Arrang *et al.*, 1995; Morisset *et al.*, 2000; Molina-Hernandez *et al.*, 2001; Gbahou *et al.*, 2006), in the  $\mu$ M range in brain slices studies (Arias-Montano *et al.*, 2001) and does not produce expected behavioral effects in H<sub>3</sub> receptor KO mice (Toyota *et al.*, 2002), and for the reasons outlined above a moderately high concentration of thioperamide (10  $\mu$ M) was used to guarantee a sufficient concentration at slices under these recording conditions. These experiments revealed that similar to observations in adult mice (Doreulee *et al.*, 2001; Ellender *et al.*, 2011) the reduction in fEPSP amplitude was not seen when histamine was superfused together with thioperamide (normalized change in fEPSP amplitude, P3-6: to 95.19  $\pm$  2.44%, P9-12: to 100.39  $\pm$  2.17% and P21-35: to 99.97  $\pm$  3.70%:  $p=0.096$ ,  $p=0.862$  and  $p=0.993$ , paired *t*-test,  $n=7/2$  mice,  $8/3$  mice and  $5/2$  mice, **Fig. 4B-D**).

In conclusion, these results show that histamine is already able to modulate corticostriatal synaptic transmission from the first postnatal days onwards and does so by acting at H<sub>3</sub> histamine receptors.

## **Histamine controls the induction of long-term synaptic plasticity at developing corticostriatal synapses**

So far our data shows that the developing striatum receives histaminergic afferents and expresses functional histamine receptors, with superfusion of histamine acutely modulating the functional properties of developing striatal circuits. Alongside acute effects on neurons and circuits we next asked whether histamine might also effect longer-term changes at striatal synapses resulting in more persistent alterations in corticostriatal circuits. Two questions were next considered: (i) do corticostriatal synapses exhibit long-term synaptic plasticity during the first weeks of postnatal development? (ii) is the induction of long-term synaptic plasticity during this period modulated by histamine? A number of studies have shown that mature corticostriatal

synapses can undergo activity-dependent prolonged changes in synaptic strength using a variety of protocols (Fino *et al.*, 2005; Kreitzer & Malenka, 2008; Kozorovitskiy *et al.*, 2012; Fisher *et al.*, 2017). We next investigated whether developing corticostriatal synapses exhibit long-term synaptic plasticity using two different stimulation patterns, consisting of a series of brief bursts at either 10Hz or 50Hz (see Methods). As these brief bursts were repeated with 200 ms intervals, i.e. at theta frequency, such stimulation patterns are often referred to as theta-burst stimulation or TBS (Larson *et al.*, 1986). TBS has been shown to be particularly effective at inducing long-term changes in synaptic strength at adult corticostriatal synapses (Hawes *et al.*, 2013), reflect activity patterns observed during naturalistic behavior (Tort *et al.*, 2008), and 10Hz or 50Hz frequencies of activity reflect physiological activity patterns found in the young developing brain (Khazipov *et al.*, 2004; Hanganu *et al.*, 2006; Yang *et al.*, 2009). Slices were kept at interface conditions as previously in the presence of the GABA<sub>A</sub> receptor antagonist SR95531 (200 nM) and cortical afferents were stimulated with a glass or bipolar stimulation electrode with fEPSP recordings made from a recording electrode placed in dorsal striatum (**Fig. 5A**). Although we observed brief post-tetanic potentiation we find at P3-6, neither 10Hz nor 50Hz TBS stimulation resulted in long-term changes in synaptic efficacy (aCSF, 10Hz:  $104.41 \pm 6.22\%$  and 50Hz:  $106.49 \pm 7.46\%$ ,  $p=0.51$  and  $p=0.42$ , paired *t*-test, both  $n=6/6$  mice, **Fig. 5B**) and this was not altered by the presence of histamine in the recording aCSF (histamine, 10Hz:  $96.25 \pm 4.04\%$  and 50Hz:  $100.20 \pm 7.47\%$ ,  $p=0.41$  and  $p=0.98$ , paired *t*-test, both  $n=5/5$  mice, **Fig. 5B**). To confirm stability of fEPSP recordings we also recorded the amplitude of fEPSPs for similar duration without TBS and find that fEPSP amplitudes stay constant over time (first 5 min:  $100.1 \pm 0.05\%$  and last 5 min:  $101.30 \pm 1.10\%$ ,  $p=0.27$ , paired *t*-test,  $n=11/10$  mice of all age ranges, **Fig. 5C**).

Similarly, in the second postnatal week, both 10Hz and 50Hz TBS stimulation did not result in significant changes in synaptic strength in aCSF (aCSF, 10Hz:  $106.01 \pm 4.19\%$  and 50Hz:  $105.74 \pm 10.29\%$ ,  $p=0.19$  and  $p=0.59$ , paired *t*-test,  $n=9/8$  mice and  $11/10$  mice, **Fig. 5D**). However, in this developmental period the presence of histamine in the recording aCSF now led to the induction of a persistent long-term potentiation of synaptic efficacy using 50Hz, but not 10Hz, TBS stimulation (histamine, 10Hz:  $94.31 \pm 5.48\%$ , vs pre-TBS  $p=0.36$ , paired *t*-test,  $n=5/5$  mice, and 50Hz:  $137.37 \pm 11.65\%$ , vs pre-TBS  $p=0.0034$ , paired *t*-test,  $n=9/5$  mice, **Fig. 5D**).

We next investigated which receptors were responsible for the observed changes in synaptic strength and hypothesized that the H<sub>3</sub> receptor, which exhibited a rapid increase in expression at P9-12, might play a role in the observed synaptic plasticity. Indeed, the long-term potentiation revealed in the presence of histamine at P9-12 was blocked by the addition of the H<sub>3</sub> receptor antagonist thioperamide (10  $\mu$ M) (50Hz:  $98.99 \pm 15.12\%$ , histamine vs histamine+thioperamide  $p=0.048$ , independent *t*-test,  $n=9/5$  mice and  $n=6/2$  mice, **Fig. 5D**). Furthermore, the observed synaptic potentiation at P9-12 in the presence of histamine was also blocked by the NMDA-receptor antagonist D-AP5 (50  $\mu$ M) (50Hz:  $62.51 \pm 17.45\%$ , histamine vs histamine+D-AP5  $p=0.0031$ , independent *t*-test,  $n=9/5$  mice and  $n=5/2$  mice, **Fig. 5D**).

Finally, in slices taken at P21-35 10Hz TBS stimulation did not lead to changes in synaptic strength similar to all other age ranges (aCSF 10Hz:  $106.91 \pm 2.30\%$  and histamine 10Hz:  $109.67 \pm 15.38\%$ , vs pre-TBS  $p=0.071$  and  $p=0.54$ , paired *t*-test,  $n=4/4$  mice and  $n=6/6$  mice, **Fig. 5E**). However, at this developmental period 50Hz TBS stimulation reliably led to the induction of long-term potentiation of the fEPSP amplitude in standard recording aCSF (aCSF 50Hz:  $146.57 \pm 12.97\%$ , vs pre-TBS  $p=0.0071$ , paired *t*-test,  $n=5/5$  mice, **Fig. 5E**) and, instead of facilitating potentiation, now the presence of histamine in the aCSF blocked the induction of long-term potentiation (histamine 50Hz:  $109.01 \pm 10.28\%$ , vs pre-TBS  $p=0.30$ , paired *t*-test,  $n=4/4$  mice, **Fig. 5E**). Similar effects were seen in slices from older animals (P35+) also where 50 Hz TBS led to potentiation (aCSF 50Hz:  $131.41 \pm 14.97\%$ , vs pre-TBS  $p=0.025$ , paired *t*-test,  $n=4/4$  mice), which was blocked by the addition of histamine to the aCSF (Histamine 50Hz:  $106.33 \pm 3.51\%$ , vs pre-TBS  $p=0.15$ , paired *t*-test,  $n=3/3$  mice). The long-term potentiation at P21-35 observed in aCSF after 50 Hz TBS was blocked by the addition of the NMDA-receptor antagonist D-AP5 (50  $\mu$ M) to the recording aCSF ( $97.61 \pm 7.39\%$ , aCSF vs aCSF+D-AP5  $p=0.0036$ , paired *t*-test,  $n=5/5$  mice and  $n=10/5$  mice, **Fig. 5E**) and the addition of the H<sub>3</sub> receptor antagonist thioperamide (10  $\mu$ M) to aCSF containing histamine could rescue the long-term potentiation ( $130.86 \pm 8.60\%$ , vs pre-TBS  $p=0.0025$ , paired *t*-test,  $n=9/3$  mice, **Fig. 5E**).

In conclusion, we find that TBS stimulation at both 10Hz and 50Hz frequency did not lead to plastic changes at corticostriatal synapses in the first postnatal week. However, in the second postnatal week brief bursts of activity at 50Hz are able to induce a long-

term increase in the synaptic strength of corticostriatal synapses, but only in the presence of histamine and dependent on both H<sub>3</sub> histamine receptors and NMDA receptors. In contrast, in the fourth postnatal week and older brief bursts of activity at 50Hz reliably induced long-term increases in synaptic efficacy, but during this period this is blocked by the addition of histamine and also dependent on H<sub>3</sub> histamine receptors and NMDA receptors.

## Discussion

The findings of the present study demonstrate that the mouse striatum receives histaminergic innervation and contains transcripts for the H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub> histamine receptors from the first postnatal weeks onwards. These receptors are functional as superfusion of histamine has acute effects on both the intrinsic electrical properties of striatal spiny projection neurons (SPNs), as well as on excitatory transmission at corticostriatal synapses. Firstly, we find that histamine modulates diverse electrical characteristics of SPNs, but during the latter stages of postnatal development mainly leads to their depolarization, and an overall reduction in their action potential output. Secondly, histamine is able to negatively modulate corticostriatal transmission by acting at H<sub>3</sub> receptors, and it does this at all developmental ages studied. Importantly, we find that histamine is able to control longer-term changes at corticostriatal synapses, as it facilitates the induction of NMDA receptor-dependent long-term synaptic plasticity during the second postnatal week, but inhibits the induction of long-term synaptic plasticity at later developmental stages, with both processes dependent on H<sub>3</sub> histamine receptors. Together, these results demonstrate that histamine is an active neuromodulator during early striatal development, and suggests that alterations in the levels of histamine can significantly affect developing corticostriatal circuits.

The striatum is the main input nucleus of the basal ganglia and in adulthood is innervated by neuromodulator-containing afferents, such as dopamine (Surmeier *et al.*, 2011), serotonin (Steinbusch, 1981), noradrenaline (Aston-Jones & Bloom, 1981) and histamine (Haas & Panula, 2003). Here we corroborate previous observations (Auvinen & Panula, 1988; Panula *et al.*, 2014) that histamine-containing afferents are found in the striatum from the second postnatal week onwards, with little to no detectable innervation during earlier periods, suggesting afferents are still maturing and have not yet reached dorsal striatum, in contrast to dopaminergic afferents (Specht *et al.*, 1981). Overall, the density of histaminergic afferents is low at all developmental periods studied, which together with the observation that varicosities only infrequently make synapses in adulthood (Takagi *et al.*, 1986), suggests that histamine might diffuse far and act at a distance from its release sites. Indeed, although low affinity organic cation transporters likely play a role in the uptake of histamine (Amphoux *et al.*, 2006), to date no specific histamine transporter or uptake

mechanism has been described in the mammalian central nervous system, but see in *Drosophila* (Borycz *et al.*, 2002; Chaturvedi *et al.*, 2014; Stenesen *et al.*, 2015; Xu *et al.*, 2015), which suggests that histamine might be degraded in the extracellular space (Schwartz *et al.*, 1991; Haas & Panula, 2003) with a possible half-life ranging in minutes (Schwartz *et al.*, 1991). Interestingly, we found transcripts for all the three major histamine receptors (H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub>) in the striatum from the first postnatal days onwards, extending on previous *in situ* work demonstrating early expression of histamine receptors in the brain (Kinnunen *et al.*, 1998; Heron *et al.*, 2001; Karlstedt *et al.*, 2001), and suggesting that released histamine could act at these receptors from birth regulating many developmental processes. Although the expression levels of the H<sub>1</sub> and H<sub>2</sub> receptors remain comparatively constant, the H<sub>3</sub> receptor exhibited a rapid developmental increase suggesting an increased ability of histamine in modulating H<sub>3</sub> receptor-dependent processes (Haas & Panula, 2003), including for example the synaptic plasticity found in this study and discussed further below. Lastly, although the extent to which the H<sub>4</sub> histamine receptor is expressed in the central nervous system is debated (Schneider & Seifert, 2016), we did not find evidence for striatal expression of these receptors as transcripts at any of the developmental age ranges studied.

To investigate whether histamine modulates developing striatal neurons and synapses, two different electrophysiological approaches were used. Firstly, we performed whole-cell patch-clamp recordings of developing striatal SPNs in combination with histamine superfusion and observed many and diverse modulatory effects on their intrinsic electrical properties. In the first postnatal week, histamine superfusion led to a significant reduction in input resistance, together with a pronounced hyperpolarization, suggestive of activation of potassium leak currents (Nisenbaum *et al.*, 1996; Weiger *et al.*, 1997; Shen *et al.*, 2007). Similar hyperpolarization has been observed in thalamic neurons and was dependent on activity at H<sub>1</sub> receptors (Sittig & Davidowa, 2001). In the second postnatal week and later we do not observe changes in input resistance, possible through developmental changes in ion channel expression (Tepper *et al.*, 1998), and instead find that histamine leads to a pronounced depolarization of SPNs (Haas & Konnerth, 1983; Ellender *et al.*, 2011). Indeed, developmental changes in ion channel expression also likely underpin our observations of a progressively decreasing input resistance and membrane time

constant across the age ranges studied, which will affect the temporal responsiveness and precision to synaptic inputs of SPNs. The histamine-mediated depolarization of striatal neurons was also observed in other studies and relied on activity at H<sub>2</sub> receptors (Ellender *et al.*, 2011), or a combination of H<sub>1</sub> and H<sub>2</sub> receptors (Munakata & Akaike, 1994; Zhuang *et al.*, 2018). Contrary to expectations, the histamine-induced depolarized state did not lead to an increase in action potential frequency upon positive current injections, which instead were significantly lowered. Similar decreases in action potential frequency have been observed in cortical interneurons and were a reflection of histamine modulating Kv3.2-containing K<sup>+</sup> channels (Atzori *et al.*, 2000), but the overall low rates of action potential firing of striatal SPNs suggests modulation through other channels mediating a prolongation of inter-spike intervals (Nisenbaum *et al.*, 1994; Baranauskas *et al.*, 2003; Shen *et al.*, 2004; Shen *et al.*, 2005). A recent elegant study demonstrated that whole-cell recordings of SPNs can lead to significant dialysis of cytosolic components altering their intrinsic firing properties and critically affecting their response to dopaminergic signaling (Lahiri & Bevan, 2020). Interestingly, clear postsynaptic effects of histamine were seen in our whole-cell patch-clamp configurations at all age ranges studied, which might have resulted from use of high-resistance pipettes, although the variance in responses could have resulted from our recording configuration. Indeed, perforated patch-clamp would be the ideal recording configuration when studying G-protein coupled receptor physiology; especially during recordings of longer duration, and concerns about dialysis of cytosolic components was one of the reasons to opt for fEPSP recordings for the long-term plasticity experiments.

Our second electrophysiological approach consisted of field recordings in acute brain slices to investigate the effect of histamine on cortically evoked glutamatergic transmission in the striatum. Histamine was able to negatively modulate the amplitude of the cortically evoked fEPSP from the first postnatal days onwards, which was dependent on H<sub>3</sub> receptors. Thus, the ability of histamine to modulate corticostriatal synapses (Doreulee *et al.*, 2001; Ellender *et al.*, 2011) is already established during the first postnatal days and the rapid increase in expression of the H<sub>3</sub> histamine receptor is likely a reflection of both an increase in the number of striatal synapses and the ability of histamine to modulate these synapses (Ellender *et al.*, 2011). It is important to note that further changes in the physiological function of histamine might occur beyond the age ranges investigated here. Indeed, precedent can



773 be found in both the neuromodulators dopamine and acetylcholine (Teicher *et al.*,  
774 1995; Lieberman *et al.*, 2018; McGuirt *et al.*, 2020), where continued dynamic  
775 changes in their function are observed at 120 days. Lastly, the use of field recordings  
776 masks possible differential effects of histamine on the two populations of striatal  
777 SPNs, the D1-expressing direct pathway SPNs and the D2-expressing indirect  
778 pathway SPNs (Day *et al.*, 2008; Gertler *et al.*, 2008). Although we cannot exclude  
779 that histamine might affect these two populations differentially during particular  
780 periods of development, previous work in more mature striatal SPNs would suggest  
781 that histamine affects both SPNs in similar ways. Indeed, they have been shown to  
782 both depolarize in response to histamine acting at H<sub>1</sub> and/or H<sub>2</sub> receptors (Ellender *et al.*,  
783 2011; Zhuang *et al.*, 2018), with a similar IC<sub>50</sub> (Zhuang *et al.*, 2018), both  
784 cortical and thalamic excitatory glutamatergic synaptic transmission are equally  
785 depressed by histamine acting at presynaptic H<sub>3</sub> receptors (Ellender *et al.*, 2011;  
786 Zhuang *et al.*, 2018), qRT-PCR experiments revealed comparable levels of expression  
787 of transcripts for the H<sub>1</sub> and H<sub>2</sub> receptors in D1 and D2 SPNs (Zhuang *et al.*, 2018)  
788 and both D1 and D2 SPNs express H<sub>3</sub> receptors (Ryu *et al.*, 1994; Pillot *et al.*, 2002).  
789 These results support the idea that, at least at more mature stages, both presynaptic  
790 and postsynaptic sites at D1 and D2 SPNs express a complement of receptors to  
791 similarly respond to histamine.

792  
793 The first postnatal weeks in the striatum are defined by a rapid increase in the number  
794 and strength of excitatory synaptic connections (Tepper *et al.*, 1998; Kozorovitskiy *et al.*  
795 *et al.*, 2012; Peixoto *et al.*, 2016; Krajewski *et al.*, 2019; Peixoto *et al.*, 2019). It has been  
796 shown that neural activity is critical in the establishment of these synaptic connections  
797 (Kozorovitskiy *et al.*, 2012) and this likely involves a form of synaptic plasticity  
798 (Calabresi *et al.*, 1992; Kreitzer & Malenka, 2008), but the exact rules that govern  
799 these processes at early periods of postnatal development are unknown. We explored  
800 the ability of brief bursts of cortical activity, mimicking naturalistic neural activity  
801 patterns (Khazipov *et al.*, 2004; Hanganu *et al.*, 2006; Yang *et al.*, 2009), to induce  
802 long-term changes in the strength of developing corticostriatal synapses. We  
803 discovered that corticostriatal synapses exhibited NMDA receptor-dependent synaptic  
804 plasticity from the second postnatal week onwards induced by brief 50Hz bursts of  
805 activity. Such NMDA receptor-dependent synaptic plasticity has also been observed  
806 with sustained higher frequency stimulation at later stages of striatal development

(Partridge *et al.*, 2000). Interestingly, this form of synaptic plasticity at corticostriatal synapses was enabled by histamine at P9-12, possibly in part through the histamine-mediated dendritic depolarization and a facilitated release of the NMDA receptor  $Mg^{2+}$  block (Calabresi *et al.*, 1992), and inhibited by histamine at older ages. Unexpectedly, both processes were dependent on  $H_3$  histamine receptors. Whereas classically the  $H_3$  receptor is thought to regulate  $G_{i/o}$  pathways leading to reduced levels of cAMP and PKA (Haas & Panula, 2003), there is evidence to suggest that in adulthood alternative isoforms of  $H_3$  receptors exist which are each differentially coupled to other intracellular pathways (e.g. MAPK pathways) (Drutel *et al.*, 2001; Nieto-Alamilla *et al.*, 2016; Rapanelli *et al.*, 2016). This, in combination with observations of the existence of  $H_3$  heteromeric channels with other G-protein coupled receptors (Ferrada *et al.*, 2009; Moreno *et al.*, 2011; Marquez-Gomez *et al.*, 2018), suggest a great complexity by which histamine acting at  $H_3$  receptors can signal to neurons and might explain the opposing effects of histamine on the observed synaptic plasticity depending on the developmental period studied. Indeed,  $H_3$  receptors can form heteromers with D1 and D2 dopamine receptors, as well as A2A adenosine receptors, at least in isolated cellular systems (Ferrada *et al.*, 2008; Moreno *et al.*, 2011; Marquez-Gomez *et al.*, 2018) which can result in complex and difficult to predict interactions and responses to histamine, dopamine and adenosine in the D1 direct pathway SPNs and the D2 indirect pathway SPNs, not least as  $H_3$  non-canonical pathways (MAPK and GSK3 $\beta$ ) also differ between D1 and D2 SPNs (Rapanelli *et al.*, 2016), and these together might affect processes such as long-term plasticity (Shen *et al.*, 2008). Furthermore, despite careful placement of stimulating electrodes and use of low levels of stimulation we cannot exclude the possibility of indirect recruitment of cholinergic interneurons and dopaminergic afferents with potential interactions between neuromodulators affecting the parameters investigated (Sulzer *et al.*, 2016; Condon *et al.*, 2019). Lastly, we cannot exclude the possibility that histamine might also have some action directly at NMDA receptors (Brown *et al.*, 1995; Haas & Panula, 2003).

In conclusion, our results show that histamine is an active neuromodulator during early postnatal development and exhibits many actions at both striatal SPNs and striatal synapses. Our results are in line with observations regarding other

840 neuromodulators and brain development, such as serotonin (Gaspar *et al.*, 2003),  
841 acetylcholine (Role & Berg, 1996) and dopamine (Kozorovitskiy *et al.*, 2015;  
842 Lieberman *et al.*, 2018) and can provide insight into the possible aetiology of  
843 neurodevelopmental disorders resulting from changes in brain histamine levels.  
844 Importantly, our results show that histamine is key in gating synaptic plasticity at  
845 developing corticostriatal synapses at an early critical period when synapses are  
846 actively remodeling (Tepper *et al.*, 1998; Kozorovitskiy *et al.*, 2015; Peixoto *et al.*,  
847 2016; Mowery *et al.*, 2017; Krajewski *et al.*, 2019; Peixoto *et al.*, 2019), and this period  
848 seems to precede later critical periods important for modulation of the intrinsic  
849 electrical properties of SPNs (Lieberman *et al.*, 2018).

## Figure legends

**Figure 1: Histaminergic innervation of the developing striatum.** (A) Schematic representation indicating developmental periods used for histamine labeling experiments. (B) Histamine immunoreactivity (red) reveals histaminergic neurons in the tuberomammillary nucleus of the hypothalamus (TMN, indicated by red square in diagram) of a P21 mouse. All sections were stained with DAPI to facilitate delineation of anatomical structures and for display purposes levels, brightness and contrast were optimized. (C) At P3-6, sparse histamine immunoreactive fiber staining was found in the cortex (top, white arrowheads), but not in the striatum (bottom). The diffuse weak signal in the striatum results from autofluorescence of blood vessels in striatum. (D) At P9-12, histamine immunoreactive fibers were found in both the striatum and the cortex (white arrowheads) and were also found at a higher density at (E) P21-35. (F) Quantification of histaminergic axonal length, fluorescence and arborizations in both cortex (white, left) and striatum (blue, right). Cortical histaminergic innervation was present at birth and axons did not exhibit a significant increase in length, fluorescence or arborizations during postnatal development (all  $p > 0.05$ ). Striatal histaminergic innervation was only detected at P9-12 (axonal length P3-6 vs P9-12,  $F(2, 6) = 31.28$   $p = 0.0074$ , and axonal fluorescence P3-6 vs P9-12,  $F(2, 6) = 5.90$   $p = 0.034$ ). ec: external capsule ANOVA: \*\*\* $p < 0.001$ , \*\* $p < 0.01$ ; \* $p < 0.05$ .

**Figure 2: Dynamic changes in transcript levels of histamine receptors in the developing striatum.** (A) The striatum of both hemispheres were dissected from acute brain slices of P3-6, P9-12 and P21-35 C57Bl/6 mice and mRNA was extracted and processed for quantitative RT-PCR. (B) Representative raw amplification curves from single quantitative RT-PCR experiments for each developmental period. The housekeeping gene  $\beta$ -actin (grey gradient) appeared at a similar cycle (Ct) throughout the different ranges, whilst the histamine receptor amplification cycles changed across development. Note the leftward shift of the histamine  $H_3$  receptor curve (blue) at P9-12 and P21-35, while the  $H_1$  (red) and  $H_2$  (green) receptor amplification curves remain relatively constant. Note also the lack of a significant amplification curve for the  $H_4$  receptor (orange). qRT-PCR amplification curves obtained from the no-RT samples (bottom panels) served as a control. (C) Representative gel of RT-PCR products showing single bands at expected sizes for each of the transcripts in the different developmental periods. Predicted band sizes are for the  $H_1$  receptor: 175bp;  $H_2$  receptor: 88bp;  $H_3$  receptor: 187bp;  $H_4$  receptor: 117bp and  $\beta$ -actin: 66bp. (D) Consistency of the  $\beta$ -actin cycle (Ct) amplification values at the three developmental periods. (E) Transcript levels of the histamine receptors in the striatum. Whilst the levels of transcripts for the  $H_1$  and  $H_2$  histamine receptors remained relatively constant during postnatal development, the levels for  $H_3$  receptor transcripts increased more than 2-fold by P9-12 and increased further by P21-35. No significant transcript levels for the  $H_4$  histamine receptor were detected. Values are means  $\pm$  SEM of 3 independent biological replicates and each biological replicate consisted of 3 technical replicates (see Methods). RFU: Relative Fluorescence Units. ANOVA: \*\* $p < 0.01$ ; \* $p < 0.05$ .

**Figure 3: Histamine modulates the intrinsic electrical properties of developing striatal SPNs.** (A) The intrinsic electrical properties of developing striatal projection neurons (SPNs) were examined by performing whole-cell patch-clamp recordings in acute brain slices from P3-6, P9-12 and P21-35 C57Bl/6 mice. (B) At P3-6, histamine

superfusion lowered the input resistance (left) and led to a hyperpolarization of SPNs (middle). The action potential frequency of SPNs induced by positive current injection was unaffected (right). (C) At P9-12, histamine did not affect the input resistance, but now led to a depolarization of SPNs and significantly decreased their action potential frequency. Little to no depolarization was observed in the absence of histamine superfusion (aCSF only; middle) during prolonged recordings from SPNs (1-5 min.:  $-71.84 \pm 0.50\text{mV}$  and 20-25 min.:  $-70.80 \pm 0.80\text{mV}$ ,  $p=0.058$ , paired  $t$ -test,  $n=7/3$ ). (D) At P21-35, histamine superfusion did not change the input resistance but led to a depolarization of SPNs and a significant decrease in action potential frequency. The indication of 'histamine' refers to start of superfusion. Values are means  $\pm$  SEM for all data sets. Statistical  $p$ -values are provided in Table 1. ns: non-significant. ANOVA and paired  $t$ -test: \*\*\* $p<0.001$ ; \*\* $p<0.01$ ; \* $p<0.05$ .

**Figure 4: Histamine negatively modulates corticostriatal transmission during early postnatal periods.** (A) Acute coronal brain slices were made from C57Bl/6 mice at the indicated age ranges and slices kept in an interface recording chamber. Cortical afferents were stimulated electrically and corticostriatal fEPSPs recorded with a glass electrode placed in dorsal striatum. Evoked fEPSPs could be blocked by the addition of the glutamatergic antagonists NBQX (20  $\mu\text{M}$ ) and D-AP5 (50  $\mu\text{M}$ , right). (B) Left, at P3-6 superfusion of histamine (10  $\mu\text{M}$ ) significantly reduced the peak amplitude of the evoked corticostriatal fEPSPs (top, two example fEPSP traces corresponding to time points indicated in the graph). Middle, the addition of the  $\text{H}_3$  receptor antagonist thioperamide (10  $\mu\text{M}$ ) to the aCSF blocked the histamine-mediated reduction in corticostriatal fEPSP amplitude. Right, the barplots summarize the effect of superfusion of histamine, histamine together with thioperamide or aCSF-only on the corticostriatal fEPSP amplitude. Plotted values are normalized means of the first 5 minutes of recording for baseline vs the last 5 minutes of recordings. At both P9-12 (C) and at P21-35 (D) superfusion of histamine also led to a significant reduction in the amplitude of the corticostriatal fEPSP, which was also blocked by co-application of the  $\text{H}_3$  receptor antagonist thioperamide and did not exhibit changes in aCSF-only controls. The indication of 'histamine' refers to start of superfusion, which precedes histamine being present at the slice. ns: non-significant. Paired  $t$ -test and Wilcoxon signed rank test: \*\* $p<0.01$ ; \* $p<0.05$ .

**Figure 5: Histamine acting at  $\text{H}_3$  receptors has opposing effects on the induction of corticostriatal synaptic plasticity depending on developmental age.** (A) Diagram of the recording configuration consisting of coronal brain sections kept at interface conditions. Electrical stimulation in the cortex generated fEPSPs as recorded with a glass electrode placed in dorsal striatum. Stable measurements of corticostriatal fEPSP amplitude were followed by brief bursts of TBS stimulation, at either 10Hz or 50Hz frequency, followed by continued measurements of corticostriatal fEPSP amplitude. (B) At P3-6, TBS at 10Hz (left) or 50Hz (right) did not result in significant changes in the amplitude of corticostriatal fEPSPs, nor was this modified in the presence of histamine (10  $\mu\text{M}$ ). (C) Corticostriatal fEPSP amplitude was stable and constant during recording periods in the absence of TBS. (D) At P9-12, 10Hz (left) or 50Hz (middle) TBS did not lead to significant changes in the amplitude of corticostriatal fEPSPs in normal aCSF, but the presence of histamine facilitated the induction of long-term potentiation after 50Hz TBS (red trace, middle, aCSF vs

aCSF+histamine,  $p=0.029$ , independent  $t$ -test,  $n=11/10$  and  $9/5$  mice). The long-term potentiation induced by 50Hz TBS was not observed with histamine in combination with the  $H_3$  receptor antagonist thioperamide (blue trace, right,  $98.99 \pm 15.12\%$ , vs pre-TBS,  $p=0.95$ , paired  $t$ -test,  $6/2$  mice) or the NMDA-receptor antagonist D-AP5 (black trace, right,  $62.51 \pm 17.45\%$ , vs pre-TBS,  $p=0.064$ , paired  $t$ -test,  $5/2$  mice). (E) At P21-35 TBS at 10Hz did not lead to long-term changes in the fEPSP amplitude in aCSF or aCSF containing histamine (left). In contrast, 50Hz TBS produces robust potentiation of the fEPSP amplitude in normal aCSF (grey trace, middle), which was reduced in the presence of histamine (red trace, middle, aCSF vs aCSF+histamine,  $p=0.047$ , independent  $t$ -test,  $n=5/5$  and  $4/4$  mice). The synaptic plasticity observed after 50Hz TBS in aCSF was blocked by the addition of the NMDA-receptor antagonist D-AP5 (dark grey trace, right, vs pre-TBS  $p=0.75$ , paired  $t$ -test,  $n=10/5$  mice) and the induction of long-term potentiation could be partly rescue by the addition of the  $H_3$  receptor antagonist thioperamide (blue trace, right, aCSF+histamine vs histamine+thioperamide  $p=0.17$ , independent  $t$ -test,  $n=4/4$  and  $9/3$  mice). ns: non-significant. Paired and independent  $t$ -test:  $**p<0.01$ ;  $*p<0.05$ .

**Table 1:** Histaminergic modulation of intrinsic electrophysiological properties of striatal spiny projection neurons across postnatal development.

**Table 2:** Dynamic changes in the properties of corticostriatal fEPSP properties across postnatal development.

**Table 3:** Histaminergic modulation of corticostriatal fEPSP properties across postnatal development.

## References

- Abdurakhmanova, S., Chary, K., Kettunen, M., Sierra, A. & Panula, P. (2017) Behavioral and stereological characterization of Hdc KO mice: Relation to Tourette syndrome. *The Journal of comparative neurology*, **525**, 3476-3487.
- Albin, R.L. (2006) Neurobiology of basal ganglia and Tourette syndrome: striatal and dopamine function. *Adv Neurol*, **99**, 99-106.
- Amphoux, A., Vialou, V., Drescher, E., Bruss, M., Mannoury La Cour, C., Rochat, C., Millan, M.J., Giros, B., Bonisch, H. & Gautron, S. (2006) Differential pharmacological in vitro properties of organic cation transporters and regional distribution in rat brain. *Neuropharmacology*, **50**, 941-952.
- Arias-Montano, J.A., Floran, B., Garcia, M., Aceves, J. & Young, J.M. (2001) Histamine H(3) receptor-mediated inhibition of depolarization-induced, dopamine D(1) receptor-dependent release of [(3)H]-gamma-aminobutyric acid from rat striatal slices. *British journal of pharmacology*, **133**, 165-171.
- Arrang, J.M., Drutel, G. & Schwartz, J.C. (1995) Characterization of histamine H3 receptors regulating acetylcholine release in rat entorhinal cortex. *British journal of pharmacology*, **114**, 1518-1522.
- Arrang, J.M., Garbarg, M., Lancelot, J.C., Lecomte, J.M., Pollard, H., Robba, M., Schunack, W. & Schwartz, J.C. (1987) Highly potent and selective ligands for histamine H3-receptors. *Nature*, **327**, 117-123.
- Aston-Jones, G. & Bloom, F.E. (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci*, **1**, 876-886.
- Atzori, M., Lau, D., Tansey, E.P., Chow, A., Ozaita, A., Rudy, B. & McBain, C.J. (2000) H2 histamine receptor-phosphorylation of Kv3.2 modulates interneuron fast spiking. *Nature neuroscience*, **3**, 791-798.
- Auvinen, S. & Panula, P. (1988) Development of histamine-immunoreactive neurons in the rat brain. *The Journal of comparative neurology*, **276**, 289-303.
- Baranauskas, G., Tkatch, T., Nagata, K., Yeh, J.Z. & Surmeier, D.J. (2003) Kv3.4 subunits enhance the repolarizing efficiency of Kv3.1 channels in fast-spiking neurons. *Nature neuroscience*, **6**, 258-266.
- Bolam, J.P. & Ellender, T.J. (2016) Histamine and the striatum. *Neuropharmacology*, **106**, 74-84.

- Borycz, J., Borycz, J.A., Loubani, M. & Meinertzhagen, I.A. (2002) tan and ebony genes regulate a novel pathway for transmitter metabolism at fly photoreceptor terminals. *J Neurosci*, **22**, 10549-10557.
- Brown, R.E., Fedorov, N.B., Haas, H.L. & Reymann, K.G. (1995) Histaminergic modulation of synaptic plasticity in area CA1 of rat hippocampal slices. *Neuropharmacology*, **34**, 181-190.
- Brown, R.E. & Haas, H.L. (1999) On the mechanism of histaminergic inhibition of glutamate release in the rat dentate gyrus. *The Journal of physiology*, **515** (Pt 3), 777-786.
- Calabresi, P., Pisani, A., Mercuri, N.B. & Bernardi, G. (1992) Long-term Potentiation in the Striatum is Unmasked by Removing the Voltage-dependent Magnesium Block of NMDA Receptor Channels. *The European journal of neuroscience*, **4**, 929-935.
- Castellan Baldan, L., Williams, K.A., Gallezot, J.D., Pogorelov, V., Rapanelli, M., Crowley, M., Anderson, G.M., Loring, E., Gorczyca, R., Billingslea, E., Wasylink, S., Panza, K.E., Ercan-Sencicek, A.G., Krusong, K., Leventhal, B.L., Ohtsu, H., Bloch, M.H., Hughes, Z.A., Krystal, J.H., Mayes, L., de Araujo, I., Ding, Y.S., State, M.W. & Pittenger, C. (2014) Histidine decarboxylase deficiency causes tourette syndrome: parallel findings in humans and mice. *Neuron*, **81**, 77-90.
- Chaturvedi, R., Reddig, K. & Li, H.S. (2014) Long-distance mechanism of neurotransmitter recycling mediated by glial network facilitates visual function in Drosophila. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 2812-2817.
- Condon, M.D., Platt, N.J., Zhang, Y.F., Roberts, B.M., Clements, M.A., Vietti-Michelina, S., Tseu, M.Y., Brimblecombe, K.R., Threlfell, S., Mann, E.O. & Cragg, S.J. (2019) Plasticity in striatal dopamine release is governed by release-independent depression and the dopamine transporter. *Nature communications*, **10**, 4263.
- Day, M., Wokosin, D., Plotkin, J.L., Tian, X. & Surmeier, D.J. (2008) Differential excitability and modulation of striatal medium spiny neuron dendrites. *J Neurosci*, **28**, 11603-11614.
- Dehorter, N., Michel, F.J., Marissal, T., Rotrou, Y., Matrot, B., Lopez, C., Humphries, M.D. & Hammond, C. (2011) Onset of Pup Locomotion Coincides with Loss of NR2C/D-Mediated Cortico-Striatal EPSCs and Dampening of Striatal Network Immature Activity. *Frontiers in cellular neuroscience*, **5**, 24.
- Doreulee, N., Yanovsky, Y., Flagmeyer, I., Stevens, D.R., Haas, H.L. & Brown, R.E. (2001) Histamine H(3) receptors depress synaptic transmission in the corticostriatal pathway. *Neuropharmacology*, **40**, 106-113.



1086 Drutel, G., Peitsaro, N., Karlstedt, K., Wieland, K., Smit, M.J., Timmerman, H.,  
1087 Panula, P. & Leurs, R. (2001) Identification of rat H3 receptor isoforms  
1088 with different brain expression and signaling properties. *Molecular*  
1089 *pharmacology*, **59**, 1-8.  
1090  
1091 Ellender, T.J., Huerta-Ocampo, I., Deisseroth, K., Capogna, M. & Bolam, J.P. (2011)  
1092 Differential modulation of excitatory and inhibitory striatal synaptic  
1093 transmission by histamine. *J Neurosci*, **31**, 15340-15351.  
1094  
1095 Ercan-Sencicek, A.G., Stillman, A.A., Ghosh, A.K., Bilguvar, K., O'Roak, B.J., Mason,  
1096 C.E., Abbott, T., Gupta, A., King, R.A., Pauls, D.L., Tischfield, J.A., Heiman,  
1097 G.A., Singer, H.S., Gilbert, D.L., Hoekstra, P.J., Morgan, T.M., Loring, E.,  
1098 Yasuno, K., Fernandez, T., Sanders, S., Louvi, A., Cho, J.H., Mane, S.,  
1099 Colangelo, C.M., Biederer, T., Lifton, R.P., Gunel, M. & State, M.W. (2010) L-  
1100 histidine decarboxylase and Tourette's syndrome. *The New England*  
1101 *journal of medicine*, **362**, 1901-1908.  
1102  
1103 Felling, R.J. & Singer, H.S. (2011) Neurobiology of tourette syndrome: current  
1104 status and need for further investigation. *J Neurosci*, **31**, 12387-12395.  
1105  
1106 Ferrada, C., Ferre, S., Casado, V., Cortes, A., Justinova, Z., Barnes, C., Canela, E.I.,  
1107 Goldberg, S.R., Leurs, R., Lluís, C. & Franco, R. (2008) Interactions between  
1108 histamine H3 and dopamine D2 receptors and the implications for striatal  
1109 function. *Neuropharmacology*, **55**, 190-197.  
1110  
1111 Ferrada, C., Moreno, E., Casado, V., Bongers, G., Cortes, A., Mallol, J., Canela, E.I.,  
1112 Leurs, R., Ferre, S., Lluís, C. & Franco, R. (2009) Marked changes in signal  
1113 transduction upon heteromerization of dopamine D1 and histamine H3  
1114 receptors. *British journal of pharmacology*, **157**, 64-75.  
1115  
1116 Fino, E., Glowinski, J. & Venance, L. (2005) Bidirectional activity-dependent  
1117 plasticity at corticostriatal synapses. *J Neurosci*, **25**, 11279-11287.  
1118  
1119 Fisher, S.D., Robertson, P.B., Black, M.J., Redgrave, P., Sagar, M.A., Abraham, W.C.  
1120 & Reynolds, J.N.J. (2017) Reinforcement determines the timing  
1121 dependence of corticostriatal synaptic plasticity in vivo. *Nature*  
1122 *communications*, **8**, 334.  
1123  
1124 Flagmeyer, I., Haas, H.L. & Stevens, D.R. (1997) Adenosine A1 receptor-mediated  
1125 depression of corticostriatal and thalamostriatal glutamatergic synaptic  
1126 potentials in vitro. *Brain research*, **778**, 178-185.  
1127  
1128 Foster, H.L.E., Small, J.D.E. & Fox, J.G.E. (1983) *The mouse in biomedical research.*  
1129 *Vol 3, Normative biology, immunology, and husbandry* edited by Henry L  
1130 *Foster, J David Small and James G Fox.* Academic Press.  
1131  
1132 Gaspar, P., Cases, O. & Maroteaux, L. (2003) The developmental role of serotonin:  
1133 news from mouse molecular genetics. *Nature reviews*, **4**, 1002-1012.  
1134

1135 Gbahou, F., Vincent, L., Humbert-Claude, M., Tardivel-Lacombe, J., Chabret, C. &  
1136 Arrang, J.M. (2006) Compared pharmacology of human histamine H3 and  
1137 H4 receptors: structure-activity relationships of histamine derivatives.  
1138 *British journal of pharmacology*, **147**, 744-754.  
1139  
1140 Gertler, T.S., Chan, C.S. & Surmeier, D.J. (2008) Dichotomous anatomical  
1141 properties of adult striatal medium spiny neurons. *J Neurosci*, **28**, 10814-  
1142 10824.  
1143  
1144 Graybiel, A.M., Aosaki, T., Flaherty, A.W. & Kimura, M. (1994) The basal ganglia  
1145 and adaptive motor control. *Science*, **265**, 1826-1831.  
1146  
1147 Grillner, S., Hellgren, J., Menard, A., Saitoh, K. & Wikstrom, M.A. (2005)  
1148 Mechanisms for selection of basic motor programs--roles for the striatum  
1149 and pallidum. *Trends in neurosciences*, **28**, 364-370.  
1150  
1151 Haas, H. & Panula, P. (2003) The role of histamine and the tuberomamillary  
1152 nucleus in the nervous system. *Nature reviews*, **4**, 121-130.  
1153  
1154 Haas, H.L. & Konnerth, A. (1983) Histamine and noradrenaline decrease calcium-  
1155 activated potassium conductance in hippocampal pyramidal cells. *Nature*,  
1156 **302**, 432-434.  
1157  
1158 Haas, H.L., Schaerer, B. & Vosmansky, M. (1979) A simple perfusion chamber for  
1159 the study of nervous tissue slices in vitro. *Journal of neuroscience methods*,  
1160 **1**, 323-325.  
1161  
1162 Hanganu, I.L., Ben-Ari, Y. & Khazipov, R. (2006) Retinal waves trigger spindle  
1163 bursts in the neonatal rat visual cortex. *J Neurosci*, **26**, 6728-6736.  
1164  
1165 Hawes, S.L., Gillani, F., Evans, R.C., Benkert, E.A. & Blackwell, K.T. (2013)  
1166 Sensitivity to theta-burst timing permits LTP in dorsal striatal adult brain  
1167 slice. *Journal of neurophysiology*, **110**, 2027-2036.  
1168  
1169 Heron, A., Rouleau, A., Cochois, V., Pillot, C., Schwartz, J.C. & Arrang, J.M. (2001)  
1170 Expression analysis of the histamine H(3) receptor in developing rat  
1171 tissues. *Mech Dev*, **105**, 167-173.  
1172  
1173 Hew, R.W., Hodgkinson, C.R. & Hill, S.J. (1990) Characterization of histamine H3-  
1174 receptors in guinea-pig ileum with H3-selective ligands. *British journal of*  
1175 *pharmacology*, **101**, 621-624.  
1176  
1177 Inagaki, N., Yamatodani, A., Ando-Yamamoto, M., Tohyama, M., Watanabe, T. &  
1178 Wada, H. (1988) Organization of histaminergic fibers in the rat brain. *The*  
1179 *Journal of comparative neurology*, **273**, 283-300.  
1180  
1181 Jafri, M.S., Moore, K.A., Taylor, G.E. & Weinreich, D. (1997) Histamine H1 receptor  
1182 activation blocks two classes of potassium current, IK(rest) and IAHP, to

1183 excite ferret vagal afferents. *The Journal of physiology*, **503 ( Pt 3)**, 533-  
1184 546.  
1185  
1186 Karlstedt, K., Senkas, A., Ahman, M. & Panula, P. (2001) Regional expression of  
1187 the histamine H(2) receptor in adult and developing rat brain.  
1188 *Neuroscience*, **102**, 201-208.  
1189  
1190 Khazipov, R., Sirota, A., Leinekugel, X., Holmes, G.L., Ben-Ari, Y. & Buzsaki, G.  
1191 (2004) Early motor activity drives spindle bursts in the developing  
1192 somatosensory cortex. *Nature*, **432**, 758-761.  
1193  
1194 Kinnunen, A., Lintunen, M., Karlstedt, K., Fukui, H. & Panula, P. (1998) In situ  
1195 detection of H1-receptor mRNA and absence of apoptosis in the transient  
1196 histamine system of the embryonic rat brain. *The Journal of comparative*  
1197 *neurology*, **394**, 127-137.  
1198  
1199 Kozorovitskiy, Y., Peixoto, R., Wang, W., Saunders, A. & Sabatini, B.L. (2015)  
1200 Neuromodulation of excitatory synaptogenesis in striatal development.  
1201 *Elife*, **4**.  
1202  
1203 Kozorovitskiy, Y., Saunders, A., Johnson, C.A., Lowell, B.B. & Sabatini, B.L. (2012)  
1204 Recurrent network activity drives striatal synaptogenesis. *Nature*, **485**,  
1205 646-650.  
1206  
1207 Krajewski, R.N., Macey-Dare, A., van Heusden, F., Ebrahimjee, F. & Ellender, T.J.  
1208 (2019) Dynamic postnatal development of the cellular and circuit  
1209 properties of striatal D1 and D2 spiny projection neurons. *The Journal of*  
1210 *physiology*, **597**, 5265-5293.  
1211  
1212 Kreitzer, A.C. & Malenka, R.C. (2008) Striatal plasticity and basal ganglia circuit  
1213 function. *Neuron*, **60**, 543-554.  
1214  
1215 Lahiri, A.K. & Bevan, M.D. (2020) Dopaminergic Transmission Rapidly and  
1216 Persistently Enhances Excitability of D1 Receptor-Expressing Striatal  
1217 Projection Neurons. *Neuron*.  
1218  
1219 Larson, J., Wong, D. & Lynch, G. (1986) Patterned stimulation at the theta  
1220 frequency is optimal for the induction of hippocampal long-term  
1221 potentiation. *Brain research*, **368**, 347-350.  
1222  
1223 Lieberman, O.J., McGuirt, A.F., Mosharov, E.V., Pigulevskiy, I., Hobson, B.D., Choi,  
1224 S., Frier, M.D., Santini, E., Borgkvist, A. & Sulzer, D. (2018) Dopamine  
1225 Triggers the Maturation of Striatal Spiny Projection Neuron Excitability  
1226 during a Critical Period. *Neuron*, **99**, 540-554 e544.  
1227  
1228 Malenka, R.C. & Kocsis, J.D. (1988) Presynaptic actions of carbachol and  
1229 adenosine on corticostriatal synaptic transmission studied in vitro. *J*  
1230 *Neurosci*, **8**, 3750-3756.  
1231

- Marquez-Gomez, R., Robins, M.T., Gutierrez-Rodelo, C., Arias, J.M., Olivares-Reyes, J.A., van Rijn, R.M. & Arias-Montano, J.A. (2018) Functional histamine H3 and adenosine A2A receptor heteromers in recombinant cells and rat striatum. *Pharmacol Res*, **129**, 515-525.
- McGuirt, A., Lieberman, O., Post, M., Pigulevskiy, I. & Sulzer, D. (2020) Coordinated postnatal maturation of striatal cholinergic interneurons and dopamine release dynamics in mice. *bioRxiv*, 2020.2004.2002.022152.
- McNaught, K.S. & Mink, J.W. (2011) Advances in understanding and treatment of Tourette syndrome. *Nat Rev Neurol*, **7**, 667-676.
- Mink, J.W. (2001) Neurobiology of basal ganglia circuits in Tourette syndrome: faulty inhibition of unwanted motor patterns? *Adv Neurol*, **85**, 113-122.
- Molina-Hernandez, A., Nunez, A., Sierra, J.J. & Arias-Montano, J.A. (2001) Histamine H3 receptor activation inhibits glutamate release from rat striatal synaptosomes. *Neuropharmacology*, **41**, 928-934.
- Moreno, E., Hoffmann, H., Gonzalez-Sepulveda, M., Navarro, G., Casado, V., Cortes, A., Mallol, J., Vignes, M., McCormick, P.J., Canela, E.I., Lluís, C., Moratalla, R., Ferre, S., Ortiz, J. & Franco, R. (2011) Dopamine D1-histamine H3 receptor heteromers provide a selective link to MAPK signaling in GABAergic neurons of the direct striatal pathway. *The Journal of biological chemistry*, **286**, 5846-5854.
- Morisset, S., Rouleau, A., Ligneau, X., Gbahou, F., Tardivel-Lacombe, J., Stark, H., Schunack, W., Ganellin, C.R., Schwartz, J.C. & Arrang, J.M. (2000) High constitutive activity of native H3 receptors regulates histamine neurons in brain. *Nature*, **408**, 860-864.
- Mowery, T.M., Penikis, K.B., Young, S.K., Ferrer, C.E., Kotak, V.C. & Sanes, D.H. (2017) The Sensory Striatum Is Permanently Impaired by Transient Developmental Deprivation. *Cell reports*, **19**, 2462-2468.
- Munakata, M. & Akaike, N. (1994) Regulation of K<sup>+</sup> conductance by histamine H1 and H2 receptors in neurones dissociated from rat neostriatum. *The Journal of physiology*, **480 ( Pt 2)**, 233-245.
- Nieto-Alamilla, G., Marquez-Gomez, R., Garcia-Galvez, A.M., Morales-Figueroa, G.E. & Arias-Montano, J.A. (2016) The Histamine H3 Receptor: Structure, Pharmacology, and Function. *Molecular pharmacology*, **90**, 649-673.
- Nisenbaum, E.S., Wilson, C.J., Foehring, R.C. & Surmeier, D.J. (1996) Isolation and characterization of a persistent potassium current in neostriatal neurons. *Journal of neurophysiology*, **76**, 1180-1194.

1279 Nisenbaum, E.S., Xu, Z.C. & Wilson, C.J. (1994) Contribution of a slowly  
1280 inactivating potassium current to the transition to firing of neostriatal  
1281 spiny projection neurons. *Journal of neurophysiology*, **71**, 1174-1189.  
1282

1283 Nissinen, M.J. & Panula, P. (1995) Developmental patterns of histamine-like  
1284 immunoreactivity in the mouse. *J Histochem Cytochem*, **43**, 211-227.  
1285

1286 Panula, P. & Nuutinen, S. (2013) The histaminergic network in the brain: basic  
1287 organization and role in disease. *Nature reviews. Neuroscience*, **14**, 472-  
1288 487.  
1289

1290 Panula, P., Sundvik, M. & Karlstedt, K. (2014) Developmental roles of brain  
1291 histamine. *Trends in neurosciences*, **37**, 159-168.  
1292

1293 Partridge, J.G., Tang, K.C. & Lovinger, D.M. (2000) Regional and postnatal  
1294 heterogeneity of activity-dependent long-term changes in synaptic  
1295 efficacy in the dorsal striatum. *Journal of neurophysiology*, **84**, 1422-1429.  
1296

1297 Peixoto, R.T., Chantranupong, L., Hakim, R., Levasseur, J., Wang, W., Merchant, T.,  
1298 Gorman, K., Budnik, B. & Sabatini, B.L. (2019) Abnormal Striatal  
1299 Development Underlies the Early Onset of Behavioral Deficits in  
1300 Shank3B(-/-) Mice. *Cell reports*, **29**, 2016-2027 e2014.  
1301

1302 Peixoto, R.T., Wang, W., Croney, D.M., Kozorovitskiy, Y. & Sabatini, B.L. (2016)  
1303 Early hyperactivity and precocious maturation of corticostriatal circuits  
1304 in Shank3B(-/-) mice. *Nature neuroscience*, **19**, 716-724.  
1305

1306 Pillot, C., Heron, A., Cochois, V., Tardivel-Lacombe, J., Ligneau, X., Schwartz, J.C. &  
1307 Arrang, J.M. (2002) A detailed mapping of the histamine H(3) receptor  
1308 and its gene transcripts in rat brain. *Neuroscience*, **114**, 173-193.  
1309

1310 Rapanelli, M., Frick, L., Bito, H. & Pittenger, C. (2017a) Histamine modulation of  
1311 the basal ganglia circuitry in the development of pathological grooming.  
1312 *Proceedings of the National Academy of Sciences of the United States of*  
1313 *America*, **114**, 6599-6604.  
1314

1315 Rapanelli, M., Frick, L., Pogorelov, V., Ohtsu, H., Bito, H. & Pittenger, C. (2017b)  
1316 Histamine H3R receptor activation in the dorsal striatum triggers  
1317 stereotypies in a mouse model of tic disorders. *Transl Psychiatry*, **7**,  
1318 e1013.  
1319

1320 Rapanelli, M., Frick, L.R., Horn, K.D., Schwarcz, R.C., Pogorelov, V., Nairn, A.C. &  
1321 Pittenger, C. (2016) The Histamine H3 Receptor Differentially Modulates  
1322 Mitogen-activated Protein Kinase (MAPK) and Akt Signaling in  
1323 Striatonigral and Striatopallidal Neurons. *The Journal of biological*  
1324 *chemistry*, **291**, 21042-21052.  
1325

1326 Role, L.W. & Berg, D.K. (1996) Nicotinic receptors in the development and  
1327 modulation of CNS synapses. *Neuron*, **16**, 1077-1085.

1328  
1329 Ryu, J.H., Yanai, K., Iwata, R., Ido, T. & Watanabe, T. (1994) Heterogeneous  
1330 distributions of histamine H3, dopamine D1 and D2 receptors in rat brain.  
1331 *Neuroreport*, **5**, 621-624.  
1332  
1333 Schneider, E.H. & Seifert, R. (2016) The histamine H4-receptor and the central  
1334 and peripheral nervous system: A critical analysis of the literature.  
1335 *Neuropharmacology*, **106**, 116-128.  
1336  
1337 Schwartz, J.C., Arrang, J.M., Garbarg, M., Pollard, H. & Ruat, M. (1991)  
1338 Histaminergic transmission in the mammalian brain. *Physiological*  
1339 *reviews*, **71**, 1-51.  
1340  
1341 Shen, W., Flajolet, M., Greengard, P. & Surmeier, D.J. (2008) Dichotomous  
1342 dopaminergic control of striatal synaptic plasticity. *Science*, **321**, 848-851.  
1343  
1344 Shen, W., Hamilton, S.E., Nathanson, N.M. & Surmeier, D.J. (2005) Cholinergic  
1345 suppression of KCNQ channel currents enhances excitability of striatal  
1346 medium spiny neurons. *J Neurosci*, **25**, 7449-7458.  
1347  
1348 Shen, W., Hernandez-Lopez, S., Tkatch, T., Held, J.E. & Surmeier, D.J. (2004)  
1349 Kv1.2-containing K<sup>+</sup> channels regulate subthreshold excitability of  
1350 striatal medium spiny neurons. *Journal of neurophysiology*, **91**, 1337-  
1351 1349.  
1352  
1353 Shen, W., Tian, X., Day, M., Ulrich, S., Tkatch, T., Nathanson, N.M. & Surmeier, D.J.  
1354 (2007) Cholinergic modulation of Kir2 channels selectively elevates  
1355 dendritic excitability in striatopallidal neurons. *Nature neuroscience*, **10**,  
1356 1458-1466.  
1357  
1358 Sittig, N. & Davidowa, H. (2001) Histamine reduces firing and bursting of  
1359 anterior and intralaminar thalamic neurons and activates striatal cells in  
1360 anesthetized rats. *Behavioural brain research*, **124**, 137-143.  
1361  
1362 Specht, L.A., Pickel, V.M., Joh, T.H. & Reis, D.J. (1981) Light-microscopic  
1363 immunocytochemical localization of tyrosine hydroxylase in prenatal rat  
1364 brain. I. Early ontogeny. *The Journal of comparative neurology*, **199**, 233-  
1365 253.  
1366  
1367 Steinbusch, H.W. (1981) Distribution of serotonin-immunoreactivity in the  
1368 central nervous system of the rat-cell bodies and terminals. *Neuroscience*,  
1369 **6**, 557-618.  
1370  
1371 Stenesen, D., Moehlman, A.T. & Kramer, H. (2015) The carcinine transporter CarT  
1372 is required in *Drosophila* photoreceptor neurons to sustain histamine  
1373 recycling. *Elife*, **4**, e10972.  
1374  
1375 Sulzer, D., Cragg, S.J. & Rice, M.E. (2016) Striatal dopamine neurotransmission:  
1376 regulation of release and uptake. *Basal Ganglia*, **6**, 123-148.

- Surmeier, D.J., Carrillo-Reid, L. & Bargas, J. (2011) Dopaminergic modulation of striatal neurons, circuits, and assemblies. *Neuroscience*, **198**, 3-18.
- Takagi, H., Morishima, Y., Matsuyama, T., Hayashi, H., Watanabe, T. & Wada, H. (1986) Histaminergic axons in the neostriatum and cerebral cortex of the rat: a correlated light and electron microscopic immunocytochemical study using histidine decarboxylase as a marker. *Brain research*, **364**, 114-123.
- Teicher, M.H., Andersen, S.L. & Hostetter, J.C., Jr. (1995) Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. *Brain research. Developmental brain research*, **89**, 167-172.
- Tepper, J.M., Sharpe, N.A., Koos, T.Z. & Trent, F. (1998) Postnatal development of the rat neostriatum: electrophysiological, light- and electron-microscopic studies. *Developmental neuroscience*, **20**, 125-145.
- Tort, A.B., Kramer, M.A., Thorn, C., Gibson, D.J., Kubota, Y., Graybiel, A.M. & Kopell, N.J. (2008) Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proceedings of the National Academy of Sciences of the United States of America*, **105**, 20517-20522.
- Toyota, H., Dugovic, C., Koehl, M., Laposky, A.D., Weber, C., Ngo, K., Wu, Y., Lee, D.H., Yanai, K., Sakurai, E., Watanabe, T., Liu, C., Chen, J., Barbier, A.J., Turek, F.W., Fung-Leung, W.P. & Lovenberg, T.W. (2002) Behavioral characterization of mice lacking histamine H(3) receptors. *Molecular pharmacology*, **62**, 389-397.
- Vanhala, A., Yamatodani, A. & Panula, P. (1994) Distribution of histamine-, 5-hydroxytryptamine-, and tyrosine hydroxylase-immunoreactive neurons and nerve fibers in developing rat brain. *The Journal of comparative neurology*, **347**, 101-114.
- Weiger, T., Stevens, D.R., Wunder, L. & Haas, H.L. (1997) Histamine H1 receptors in C6 glial cells are coupled to calcium-dependent potassium channels via release of calcium from internal stores. *Naunyn-Schmiedeberg's archives of pharmacology*, **355**, 559-565.
- Xu, Y., An, F., Borycz, J.A., Borycz, J., Meinertzhagen, I.A. & Wang, T. (2015) Histamine Recycling Is Mediated by CarT, a Carcinine Transporter in Drosophila Photoreceptors. *PLoS Genet*, **11**, e1005764.
- Yael, D., Vinner, E. & Bar-Gad, I. (2015) Pathophysiology of tic disorders. *Mov Disord*, **30**, 1171-1178.

1425 Yang, J.W., Hanganu-Opatz, I.L., Sun, J.J. & Luhmann, H.J. (2009) Three patterns of  
1426 oscillatory activity differentially synchronize developing neocortical  
1427 networks in vivo. *J Neurosci*, **29**, 9011-9025.  
1428

1429 Yu, Y.C., Satoh, H., Wu, S.M. & Marshak, D.W. (2009) Histamine enhances voltage-  
1430 gated potassium currents of ON bipolar cells in macaque retina. *Invest*  
1431 *Ophthalmol Vis Sci*, **50**, 959-965.  
1432

1433 Zecharia, A.Y., Yu, X., Gotz, T., Ye, Z., Carr, D.R., Wulff, P., Bettler, B., Vyssotski, A.L.,  
1434 Brickley, S.G., Franks, N.P. & Wisden, W. (2012) GABAergic inhibition of  
1435 histaminergic neurons regulates active waking but not the sleep-wake  
1436 switch or propofol-induced loss of consciousness. *J Neurosci*, **32**, 13062-  
1437 13075.  
1438

1439 Zhuang, Q.X., Xu, H.T., Lu, X.J., Li, B., Yung, W.H., Wang, J.J. & Zhu, J.N. (2018)  
1440 Histamine Excites Striatal Dopamine D1 and D2 Receptor-Expressing  
1441 Neurons via Postsynaptic H1 and H2 Receptors. *Mol Neurobiol*, **55**, 8059-  
1442 8070.  
1443  
1444