Histamine H3 receptor antagonism modulates autism-like hyperactivity but not repetitive behaviors in BTBR T+Itpr3tf/J inbred mice

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ARTICLE INFO

Keywords:
Repetitive behaviors
Autism spectrum disorders
Histamine H3 receptor
Behavioral pharmacology
BTBR T+Itpr3tf/J mice

ABSTRACT

Background: Autism spectrum disorders (ASDs) are a group of neurodevelopmental conditions defined by behavioral deficits in social communication and interactions, mental inflexibility and repetitive behaviors. Converging evidence from observational and preclinical studies suggest that excessive repetitive behaviors in people with ASD may be due to elevated histaminergic H3 receptor signaling in the striatum. We hypothesized that systemic administration of pharmacological histamine H3 receptor antagonists would attenuate the expression of repetitive behaviors in the BTBR T+Itpr3tf/J (BTBR) mouse inbred strain, an established mouse model presenting autism-like repetitive behaviors and novelty-induced hyperactivity. We further aimed to investigate whether agonism of the histamine H3 receptor would be sufficient to induce repetitive behaviors in the C57BL/6J control mouse strain.

Methods: Different doses of H3 receptor agonists (i.e., (R)-α-methylhistamine and immethridine) and H3 receptor antagonists/inverse agonists (i.e., ciproxifan and pitolisant) were administered via intraperitoneal (i.p.) injection in male mice to characterize the acute effects of these compounds on ASD-related behavioral readouts.

Results: The highly selective H3 receptor agonist immethridine significantly increased the time spent in stereotypic patterns in C57BL/6J mice, but this effect appeared to be driven by general sedative properties of the compound. High doses of pitolisant significantly decreased locomotor hyperactivity in novel environments in BTBR mice, without significant effects on repetitive behaviors.

Conclusions: Based on our findings, we conclude that acute H3 receptor manipulation mainly affected general motor activity levels in novel environments. Small changes in stereotyped behaviors were observed but appeared to be driven by altered general activity levels.

1. Introduction

Autism spectrum disorder (ASD) refers to a group of neurodevelopmental conditions characterized by restricted and repetitive patterns of behavior and difficulties with social communication and interactions (Am. Psychiatr. Assoc., 2013). Caregivers commonly report that repetitive behavior symptoms are among the most challenging aspects of ASD in daily life, as these symptoms are related to distress in response to relatively minor changes or transitions (Boyd et al., 2012). Moreover, the severity of repetitive behavior symptoms at preschool age has been associated with poor outcome later in life (Hollocks et al., 2011b, 2011a; Rothwell et al., 2014). Indeed, histamine H3 receptor signaling via the basal ganglia, which is the primary brain circuitry associated with repetitive behaviors in people with ASD (Fuccillo, 2016; Langen et al., 2016). Interestingly, these findings largely overlap with frequently observed comorbidities in people with ASD (Humphreys et al., 2014; Kas et al., 2014). Recent studies have further linked histaminergic signaling via the H3 receptor with autism-like repetitive behaviors based on converging evidence from genetic association studies, post-mortem brain analyses and experimental animal models (Baronio et al., 2015; Eissa et al., 2018; Molenhuis et al., 2018; Rapanelli et al., 2017; Wright et al., 2017). These findings align with known properties of the histamine H3 receptor in basal ganglia, which is the primary brain circuitry associated with repetitive behaviors in people with ASD (Fuccillo, 2016; Langen et al., 2011b, 2011a; Rothwell et al., 2014). Indeed, histamine H3 receptor signaling regulates ventral striatal dopamine release, and is a known physiological functions, including circadian rhythmicity, thermogenesis, energy metabolism, locomotor activity, sensory sensitivity and neuronal hyperexcitability (Haas et al., 2008; Sadek et al., 2016).

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https://doi.org/10.1016/j.pbb.2021.173304
Received 2 November 2021; Received in revised form 24 November 2021; Accepted 24 November 2021
Available online 29 November 2021
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differential modulator of mitogen-activated protein kinase (MAPK) and Akt signaling in striatogranin and striatopallidal neurons (Bolam and Ellender, 2016; Nieto-alamilla and Marquez-gomez, 2016; Rapanelli et al., 2016; Varaschin et al., 2018).

We previously characterized the expression of stereotypic exploratory patterns in the BTBR T+Itpr3tf/J (BTBR) mouse inbred strain, an established model for autism-like repetitive behaviors (Karvat and Kimchi, 2014; Molenhuis et al., 2018, 2014; Moy et al., 2008). In addition to these stereotypic behaviors, mice of this strain also display novelty-induced hyperactivity combined with reduced locomotor activity at baseline levels, as well as repetitive grooming and cognitive inflexibility (Molenhuis et al., 2018, 2014). Based on a genetic association study for stereotyped exploratory patterns in a heterogeneous population of mouse recombinant inbred lines, we hypothesized that histamine H3 receptor antagonism would be an effective strategy to attenuate the expression of repetitive behaviors across diverse genetic backgrounds, including in the BTBR T+Itpr3tf/J (BTBR) mouse inbred strain.

In this study, we set out to investigate the acute effects on repetitive behaviors in BTBR T+Itpr3tf/J mice of systemic administration of ciproxifan, a highly potent H3 receptor antagonist/inverse agonist with known attention-promoting effects (Ligneau et al., 1998), and of pitolician, an H3 receptor inverse agonist recently approved by the European Medicines Agency (EMA) for the treatment of excessive daytime sleepiness (Kollb-Sielecka et al., 2017). We further aimed to investigate whether acute stimulation of the histamine H3 receptor via administration of (R)-α-methylhistamine (RAMH), a classical H3 receptor agonist, and of immethridine, a highly selective H3 receptor agonist, would be sufficient to induce stereotyped exploratory patterns and repetitive grooming behaviors in C57BL/6J mice.

2. Methods

2.1. Animals

Breeding pairs of C57BL/6J (JAX stock #000664) and BTBR T+Itpr3tf/J (JAX stock #002282) mice were originally ordered from The Jackson Laboratory (Bar Harbor, Maine, USA) via Charles River Europe (Den Bosch, The Netherlands) and further bred at the University of Groningen, The Netherlands. Male mice were weaned at the age of 4 weeks, ear punched for identification purposes and housed with litter mates in groups of 2–4 mice per cage. Mice were maintained under a 12:12 light/dark cycle, controlled temperature (21 ± 1 °C) and humidity (55 ± 5%) and with ad libitum access to food and water. All animals were kept on standard Aspen bedding and had access to shredded cardboard nesting material and a cardboard tube as enrichment. At the start of the experiment, all mice were 11 weeks of age (adult). All experiments were conducted following the approval of the animal experiment ethics committee of the University of Groningen and according to the institutional guidelines that are in full compliance with the EU Directive (2010/63/EU). Experiments were carried out and the manuscript was prepared following the ARRIVE guidelines for animal research (Kilkenny et al., 2010). Only male mice were used since ASD is highly male dominated (3:1 ratio).

2.2. Experimental design and procedures

Pharmacological compounds in this study were purchased from Tocris Bioscience (Abingdon, UK) including H3 receptor inverse agonist pitolician and the H3 receptor agonists RAMH and immethridine. Ciproxifan was purchased from Sigma-Aldrich (Saint Louis, MO, USA). Mice were injected intra peritoneally (i.p.) 30 min before behavioral testing following a randomized block design to test three different doses and saline as vehicle control per animal with one-week wash-out periods between behavioral assessments. The injected volume was 0.1 ml/10 g of body weight. Four groups of mice (n = 12 per group) were exposed to pharmacological compounds acting on the H3 receptor; two H3 antagonists were tested at different doses in BTBR T+Itpr3tf/J mice, and two H3 agonists were tested at different doses in C57BL/6J mice (also see Supplementary Figs. S1–3). Acute injection with H3 receptor antagonist ciproxifan at 3 mg/kg was previously shown to attenuate elevated repetitive behavior levels in the valproic acid model for ASD with an effect size of 2.2 (Baronio et al., 2015). In our study, a sample size of n = 12 per batch was used to achieve 90% power to detect effects with size >1.3 after correction for multiple testing (based on a paired t-test and Dunnett’s post-hoc correction for comparing three doses versus saline). To assess more subtle effects of H3 receptor inverse agonist pitolician on repetitive behaviors, two additional, larger batches of BTBR T+Itpr3tf/J and C57BL/6J mice were exposed to pitolician (n = 32 per group, sufficient to achieve 90% power to detect effect sizes >0.6 in a paired t-test). Safe dosages and route of injection were selected based on previous studies in mice (Baronio et al., 2015; Brabant et al., 2016; Rapanelli et al., 2017; Shi et al., 2017). The investigators were blinded to the compound and dose during the injections.

2.3. Behavioral assessments

Behavioral testing was performed to assess the acute effects of H3 receptor pharmacological manipulation on stereotyped exploratory patterns for a duration of 10 min in a type II Makrolon cage with bedding and four novel objects as previously described (Molenhuis et al., 2018). Locomotor activity in this testing environment was assessed based on the total distance moved using Ethovision XT (Noldus IT, Wageningen, The Netherlands). Time in stereotyped patterns was calculated after correction for activity as previously reported for BTBR T+Itpr3tf/J mice using Theme software (Noldus IT, Wageningen, The Netherlands). In short, exploratory patterns are quantified by testing whether spatial bins of locomotor activity occur in particular sequences (‘patterns’) over time at a probability greater than chance. Following the identification of such recurring patterns, the score for stereotyped exploratory patterns is defined as the total percentage of time the animal spent in patterns (Bonasera et al., 2008; Molenhuis et al., 2018). After the exposure to the novel object environment, animals were transferred into a transparent viewing jar (21 cm × 30 cm) to assess grooming behavior. The time spent grooming was scored manually as previously reported (Molenhuis et al., 2014) for a total duration of 5 min after 10 min of habituation using the Observer XT (Noldus IT, Wageningen, The Netherlands). All behavioral testing was performed at least 2 h after the start of the dark phase. The investigators remained blinded to the compound and dose during the experiments and behavioral analyses.

2.4. Statistical analyses

All data were analyzed using R Studio version 1.1.463 for Mac (R core team, 2016). Data are plotted as the mean ± standard error of the mean with violin plots generated using the ‘ggplot2’ package representing probability density of the data at different values. Data were checked prior to statistical tests being carried out to ensure that test assumptions were met. All data were obtained from randomized block designs and analyzed using a repeated measures ANOVA with dose as within-subjects variable, followed by Dunnett’s post hoc tests to correct for multiple testing unless otherwise stated. All data points were included in the analyses. For all tests, a p-value <0.05 was considered significant. Cohen’s d effect sizes were calculated based on the difference between the means divided by the pooled standard deviation using the ‘rstatix’ package in R.
3. Results

3.1. Effects of H3 receptor agonists to induce repetitive behaviors in C57BL/6J mice

We first aimed to investigate whether systemic administration of H3 receptor agonists would be sufficient to induce repetitive behaviors in C57BL/6J control mice. Following a cross-over design, we did not observe any statistically significant effect of the classical H3 receptor agonist RAMH on either locomotor activity, stereotyped exploratory patterns, or on repetitive grooming behavior at doses of 5, 20 or 45 mg/kg (Fig. 1a–c).

In contrast, the selective H3 receptor agonist imemethridine significantly decreased the distance C57BL/6J mice moved and post hoc comparisons with correction for multiple testing indicated significant reductions in locomotor activity at doses of 20 and 45 mg/kg (Fig. 1d). The reduction in locomotor activity at the high dose of 45 mg/kg was associated with an increased time spent in stereotypic patterns, as well as a reduction in grooming behaviors (Fig. 1e and f). These effects appeared to be driven by general sedative properties, since mice with increased stereotypic patterns at high doses of imemethridine were characterized by very low levels of activity (Fig. 2a and b).

3.2. Effects of H3 receptor inverse agonists/agonists to attenuate repetitive behaviors in BTBR T+Ipr3tf/J mice

Next, we tested whether systemic administration of potent H3 receptor inverse agonist/antagonist ciproxifan would attenuate locomotor hyperactivity and repetitive behaviors in the BTBR T+Ipr3tf/J mouse inbred strain model for ASD. In this experiment, we did not observe any statistically significant effect on locomotor hyperactivity, stereotyped exploratory patterns or grooming behavior at different doses of ciproxifan using a cross-over design (Fig. 3a–c).

By contrast, the H3 receptor inverse agonist pitolisant significantly suppressed locomotor hyperactivity in BTBR T+Ipr3tf/J mice at a high dose of 30 mg/kg (Fig. 3d). This effect was concurrent with a trend towards less grooming behavior at 30 mg/kg (Fig. 3f). In an additional, larger set of animals, we tested whether 10 mg/kg pitolisant may have a subtle effect on repetitive grooming behavior in the absence of influencing locomotor activity. In this experiment, 10 mg/kg pitolisant led to a statistically significant reduction of locomotor activity with a non-significant trend of reduced repetitive grooming behavior in BTBR T+Ipr3tf/J mice. 

![Fig. 1. Effects of H3 receptor agonists on locomotor hyperactivity, stereotyped exploratory patterns and repetitive grooming behavior. Effects of 5, 20 and 45 mg/kg RAMH administered via i.p. injection on a) locomotor activity (rmANOVA, p = 0.366 (n.s.)), b) stereotyped exploratory patterns (rmANOVA, p = 0.378 (n.s.)), and c) grooming behavior (rmANOVA, p = 0.337 (n.s.)). Effects of 5, 20 and 45 mg/kg immethridine on d) locomotor activity (rmANOVA, p = 0.0014; post hoc adjusted p = 0.002 for 20 mg/kg with Cohen’s d = 0.928 (95% CI for Cohen’s d = 0.19–4.43) and p < 0.001 for 45 mg/kg with Cohen’s d = 1.17 (95% CI for Cohen’s d = 0.65–2.43)), e) stereotyped exploratory patterns (rmANOVA, p = 0.023; post hoc adjusted p = 0.0412 for 45 mg/kg with Cohen’s d = 0.628 (95% CI for Cohen’s d = 0.09–1.46)), and f) grooming behavior (rmANOVA, p = 0.0138; post hoc adjusted p = 0.0075 for 45 mg/kg with Cohen’s d = 1.03 (95% CI for Cohen’s d = 0.46–2.47)). Violin plots represent the mean ± standard error of the mean, as well as probability density of the data at different values, n = 12 C57BL/6J mice per group.](image-url)
T+Itpr3tf/J (Fig. 4a and b). The effect of 10 mg/kg pitolisant on locomotor activity was not seen in C57BL/6J mice (data not shown).

Pitolisant did not influence the time spent in stereotyped patterns in BTBR T+Itpr3tf/J mice, although a trend was observed at the lowest dose of 3 mg/kg (Fig. 3e). To test any possible effect of very low doses of pitolisant, we performed an additional experiment in the same set of BTBR animals with a dose of 1 mg/kg but failed to observe any effect on stereotyped exploratory patterns (Fig. 4c). In a subsequent larger batch of animals, pitolisant did also not influence stereotyped exploratory patterns at a dose of 3 mg/kg (Fig. 4d).

Fig. 2. Excessive time in stereotypic patterns following high dose of immethridine in C57BL/6J mice coincides with impaired locomotor activity. Correlation plots display the time spent in stereotypic patterns and distance moved following i.p. injection with either a) saline or b) 45 mg/kg immethridine. Note that four out of five animals with >30% time spent in patterns at 45 mg/kg immethridine display very low levels of locomotor activity (<300 cm in 10 min). Graphs display linear regression lines and Spearman’s rank correlation coefficients.
we did not observe a reduction of locomotor activity by 10 mg/kg pitolisant in an additional sample of C57BL/6J mice.

The attenuation of hyperactivity in BTBR T-Itpr3tf/J mice was observed for high doses of pitolisant (i.e., 10 and 30 mg/kg), but not for ciproxifan. Although pitolisant and ciproxifan differ in their H3 receptor selectivity, we argue that this lack of effect on motor activity levels for ciproxifan is likely due to the relatively low maximum dosage that was used in the present study, which was selected based on previously reported safe dosages of ciproxifan in mice (i.e., 3 mg/kg) (Baronio et al., 2015; Brabant et al., 2016; Ligneau et al., 1998). Clearly, these two compounds are H3 ligands, as studies have shown effective H3 blockade through H3 receptor inverse agonist- and partial agonist-induced dipsogenic models (Fox et al., 2002; Łazewska et al., 2018), but their contributions to motor activity levels seem to be dose dependent.

Previous studies have shown that RAMH injected i.p. at dosages that were also used in the present study are sufficient to induce repetitive behaviors in a mouse model for tic disorders (Rapanelli et al., 2017). The lack of behavioral effects in C57BL/6J mice in our study may be due to limited bioavailability and extensive metabolism, in combination with relatively low dosing based on concerns for potential cardiovascular side-effects mediated through α-2 receptors (Leurs et al., 2005). Immethridine shows a 300-fold selectivity over the related human H4 receptor (Leurs et al., 2005) and resulted in profound behavioral effects at higher dosages. Both pitolisant and ciproxifan are known to be brain-penetrant, yet we did not observe any effects of 3 mg/kg doses on repetitive behaviors, as previously shown for i.p. injection of ciproxifan in
the valproic acid mouse model for ASD (Baronio et al., 2015; Ligneau et al., 2007).

The behavioral effects of histamine H3 receptor ligands are likely mediated via neuronal activity of diverse brain circuitries characterized by auto- or heteroreceptor functioning (Bolam and Ellender, 2016; Nieto-alamilla and Márquez-gómez, 2016). The genetic G293D polymorphism that we previously associated with stereotyped exploratory patterns in a heterogeneous population of mouse recombinant inbred lines has been linked with differential Hrh3 isoform expression and may thus have varied impact across diverse cell types and associated behaviors (Krementsov et al., 2013; Molenhuis et al., 2018). Therefore, cell-type specific manipulations of the H3 receptor may be required to pinpoint the exact role of H3 receptor signaling in the context of repetitive behaviors and novelty-induced hyperactivity. This would allow disentangling H3 receptor-mediated effects on general activity from its possible therapeutic effects on autism-relevant behaviors.

Data access

Raw data are available from the corresponding authors upon request.

CRediT authorship contribution statement

RTM and MJHK designed the study. RTM and LH conducted the experiments, acquired the data and performed the statistical analyses. RTM, LH and MJHK interpreted the data. RTM wrote the manuscript. MJHK critically reviewed and commented on the initial draft of the manuscript. All authors contributed to and approved the final manuscript.

Declaration of competing interest

There are no conflicts of interest related to the manuscript for any of the authors.

Acknowledgements

RTM was supported by an FSE Postdoctoral Fellowship in Behavioral Neuroscience at the University of Groningen. The results leading to this publication have received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777394 for the project AIMS-2-TRIALS. This Joint Undertaking receives support from the IMI 2JU.

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