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Enhanced central histaminergic transmission attenuates compulsive-like behavior in mice

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ABSTRACT

Present investigation demonstrated the effect of central histaminergic transmission on the compulsive-like marble burying and spontaneous alteration behavior (SAB) in mice. Result demonstrates that on enhancement of endogenous histaminergic transmission in mice achieved by central (i.c.v.) administration of histamine or central histamine neuronal releaser, H_3 receptor antagonist or on intraperitoneal (i.p.) administration of histamine precursor, L-histidine significantly attenuated the number of marble buried in marble burying behavior (MBB) test as well as obliterated the persistent behavior induced by 5-HT_{1A} receptor agonist, 8-OH-DPAT in T-Maze test. Furthermore, central injection of histamine H_1 receptor agonist, FMPH or H_2 receptors agonist, amthamine also attenuated the MBB in mice. On the other hand, prior i.c.v administration of H_1 but not H_2 receptor antagonist attenuated the effects exhibited in MBB test on mice by all the above agents capable of enhancing the endogenous central histaminergic transmission. Thus, the results of the present investigation delineate the attenuating effect of central histaminergic transmission predominantly via H_1 receptor on compulsive-like behavior in mice.

1. Introduction

Recurrent obsessions and/or compulsion is commonly observed in many highly debilitating neuropsychiatric conditions like obsessive-compulsive disorders (OCD), autism (Chang et al., 2017) and Tourette syndrome (TS) or Tic disorder (Ercan-Sencicek et al., 2010; Rapanelli et al., 2017). Recently, studies from our group (Umathe et al., 2009a, 2009b, 2011, 2012) and others (Chakrabarty et al., 2005; Denys et al., 2004; Salunke et al., 2014) have identified many targets including GnRH, neurosteroids, endocanabinoids, glutamate, nitric oxide and dopamine that can be implicated in the modulation of compulsive behavior. However, the application of these targets for the management of compulsive-like behavior is still under scrutiny. Moreover, anti-OCD drugs like serotonin re-uptake inhibitors (SSRI) have shown to mitigate compulsive-like symptoms only in 40–60% patients suffering from OCD (Pallanti and Quercioli, 2006). Therefore, it is reasonable to contemplate that multiple neurotransmitter systems might be probably involved in the regulation of obsessive compulsive and persistent behavior. Thus, suggesting a need of newer biological targets for the effective management of obsessive-compulsive behavior (OCB).

Clinical findings indicated a defect in the neurocircuitry of cortico-striatal-thalamic-cortical loop in the patients exhibiting the compulsive-like symptoms (Rosenberg et al., 2001; Szeszko et al., 1999). Interestingly, literature review points toward a strong presence of the histaminergic system in the brain regions that are reported to be involved in the induction of compulsive-like symptoms in many disorders. Accumulating evidence favours the suggestion that histamine might play a pivotal role as a neurotransmitter or neuromodulator in the central nervous system via its receptor subtypes i.e. H_1, H_2, H_3 or H_4 (Hill, 1987; Panula and Nuutinen, 2013). It is reported that the posterior part of the hypothalamus i.e. the tuberomamillary nucleus (TMN) contains highest density of histaminergic neurons that projects extensively and innervate nearly all regions of the brain (Bolam and Ellender, 2016; Panula et al., 1984; Watanabe et al., 1983). Especially, in the context of the present study, histaminergic neurons heavily innervate the cortico-limbic structures, including the septum, hippocampus, basal ganglia, pery acquiductal grey (PAG), amygdala and as well as monoaminergic clusters (Ellender et al., 2011; Haas et al., 2008; Hill et al., 1997; Hill and Young, 1980; Martinez-Mir et al., 1990; Pillot et al., 2002). Thus, there exist a functional innervation of histaminergic neurons with the structures,

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dysfunction of whom may lead to compulsive and repetitive symptoms (Graybiel and Rauch, 2000; Saxena et al., 1998) and also expression of the histamine receptors in the brain areas dysfunctional in OCD i.e. thalamus, caudate, putamen, cortex amygdale, striatum, SNr, hippocampus and globus pallidus (GP) (Bolam and Ellender, 2016; Cumming and Gjedde, 1994; Hill et al., 1997; Pillot et al., 2002; Pollard et al., 1993).

Indeed, some previous investigations have shown the relevance of central histaminergic transmission in the modulation of symptoms observed in some of the compulsive-spectrum disorders. Central histamine deficiency due to a rare mutation in the key enzyme involved in histamine synthesis i.e. histidine decarboxylase (HDC) has been linked with the TS (Baldan et al., 2014; Ercan-Sencicek et al., 2010) and increased repetitive/grooming behavior (Rapanelli et al., 2017). Therefore, intrigued by the above neuroanatomical evidences, the present investigation attempted to assess the effect of histamine or its receptor ligands on the OCB by employing two well established rodent behavioral paradigms that exhibits compulsive-like activity i.e. marble burying behavior (MBB) test (Joel and Klavir, 2006; Umathe et al., 2012) and spontaneous alternation of behavior (SAB) (Umathe et al., 2009b; Yadin et al., 1991) in mice.

2. Materials and methods

2.1. Animals and experimental conditions

The experiments were carried out in strict accordance with the guidelines approved by the Institutional Animal Ethics Committee (IAEC) under the supervision of Committee for the Purpose of Control and Supervision of Experiments on animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi, India. The investigations were carried out on male Swiss mice (22–25 g of age 10–12 weeks) housed in a group of 6 per cage in an opaque polypropylene cage and maintained at 25 ± 2 °C; relative humidity 55–65 ± 5% under 12:12 h light and dark cycle (light cycle: 07:00–19:00 h) with free access to rodent chow and water *ad libitum*. Twelve hours before performing the experiment, animals were acclimatized to the experimental room and the experiments were conducted in a noise attenuated chamber between 08:00 and 15:00 h. Separate group (n = 6) of mice was used for each set of experiments. At the beginning of all protocols, the animals were naïve to drug treatment and experimentations.

2.2. Intracerebroventricular (i.c.v.) cannulation

The i.c.v. cannulations were carried out as described earlier (Jain et al., 2015; Umathe et al., 2008; Verma and Jain, 2016). In brief, each mouse was anaesthetized with ketamine (100 mg/kg, s.c.) and xylazine (5 mg/kg, s.c.) and a guide cannula (24 gauge) was stereotaxically implanted as per the coordinates from (Paxinos and Franklin, 2001)(AP −0.22 mm; ML +1.2 mm; and DV +2.5 mm; related to bregma). The guide cannula was secured to skull using mounting screws and dental cement. A stainless steel dummy cannula was used to occlude the guide cannula, when not in use. Thereafter, the animals were allowed to recover for a week under the cover of antibiotic, cefotaxim (50 mg/kg/day, s.c.), and were also treated with carprofen (5 mg/kg, s.c.) once every 24 h for up to 5 days in order to relieve the pain. Injections were made using a microliter Hamilton syringe connected to internal cannula (41 gauges) by polyethylene tubing and a volume of 5.0 μl was administered over a period of 2 min into the right lateral ventricle. The injection cannula was left in place for further 1 min before being slowly withdrawn to avoid back flow. At the end of all experiments involving i.c.v. administration, dilute India ink was injected (5 μl, i.c.v.) and to isolate the brain, the animals were euthanized by pentobarbitone over dose to ascertain the correctness of cannula placement. Only data from animals showing uniform distribution of ink into lateral ventricles were used for statistical analysis.

2.3. Drugs and solutions

The drugs i.e. histamine dihydrochloride, histamine precursor, L-histidine dihydrochloride, histamine H_1 selective receptor agonist, 2-(3-trifluoromethylphenyl)histamine (FMPH) (2138-fold more selective to H_1 than on H_2 receptors) (Leschke et al., 1995), H_2 selective receptor agonist, amthamine (Eriks et al., 1992) and H_3 receptor antagonist/inverse agonist, thioperamide maleate (Arrang et al., 1987) and (R)-(+)-8-Hydroxy-DPAT hydrobromide (2-Dipropylamino-1,2,3,4-tetrahydronaphthalene) (8-OH-DPAT), a 5-HT_{1A} receptor agonist were procured from Sigma-Aldrich, USA. On the other hand, H_1 receptor antagonist, cetirizine hydrochloride (In binding studies, the affinity of cetirizine was found to be at least 500 times in favour of histamine H_1 receptors vs. histamine H_2 or H_3 receptors (Gillard et al., 2002) and the selective H_2 receptor antagonist, ranitidine hydrochloride (Bradshaw et al., 1979) were generously gifted by Zim Lab. Limited, Nagpur, India. L-histidine was dissolved in 0.9% saline solution and administered via intraperitonial (i.p.) route. On the other hand, those drugs injected via i.c.v. route were dissolved in artificial cerebrospinal fluid (aCSF) of following composition: 0.2 M NaCl, 0.02 M NaH2Co3, 2 mM KCl, 0.5 mM KH2PO4,1.2 mM CaCl2, 1.8 mM MgCl2, 0.5 mM Na2SO4, 5.8 mM D-glucose (Dissolved in double distilled water). The doses of all the drugs were calculated as free base. The doses of histaminergic agents are adopted from the preliminary protocol from our lab (Jain et al., 2015; Verma and Jain, 2016) or from previous reports (Farzin et al., 2002; Malmberg-Aiello et al., 1994; Serafim et al., 2012).

2.4. Apparatus and procedures

2.4.1. Marble-burying behavior (MBB)

The testing apparatus consisted of polycarbonate cages (38 cm × 21 cm × 20 cm) filled to a depth of 5 cm with sawdust bedding. Prior to each test, 20 small glass marbles (diameter ~10 mm) were evenly spaced and arranged in a grid-like fashion across the surface of the bedding. The apparatus was placed 2.0 m below a video camera in the sound-attenuated room lighted by white light (40 lx) (Umathe et al., 2009b). The marble-burying behavior was assessed by the method described earlier by (Njung'e and Handley, 1991) with slight modifications (Umathe et al., 2009b). In brief, mice were individually placed 30 min before the test session for pre-exposure of 5 min to the sawdust without the marbles to avoid novelty-seeking behavior during the test. In the test session, a mouse was placed in the centre of the marble-containing box to which it was previously subjected for acclimatization. Fifteen minutes later, the mouse was taken out from the box, and the number of marbles buried was counted. A marble was considered 'buried' only if two-third of it is covered with sawdust. The total number of marbles buried was considered as an index of obsessive compulsive behavior. The behavior of the mice during the test session was recorded by the video camera and was analyzed by an observer blind to experimental treatments.

2.4.2. T-maze test: Spontaneous alternation of behavior (SAB)

The T-maze apparatus consisted of a black plexiglass with all arms including start box and the two goal boxes of dimension 50 × 10 × 30 cm. Black Plexiglas doors separated the start box and the goal boxes from the main body of the maze. A small plastic cup