Pharmacology, Biochemistry and Behavior 139 (2015) 59–66

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

# Contribution of the central histaminergic transmission in the cataleptic and neuroleptic effects of haloperidol

Nishant S. Jain *, Lakshyapati Tandi, Lokesh Verma

*Department of Pharmacology, Institute of Pharmaceutical Sciences, Guru Ghasidas University (A Central University), Koni, Bilaspur, Chhattisgarh, India*

ARTICLE INFO

*Article history:*
Received 9 May 2015
Received in revised form 16 September 2015
Accepted 7 October 2015
Available online 9 October 2015

*Keywords:*
Antipsychotic effects
Catalepsy
Conditioned avoidance chamber
Haloperidol
Histamine
Neuroleptics

ABSTRACT

The antipsychotic properties of haloperidol are primarily attributed to its ability to block dopamine $D_2$ receptors. Histaminergic transmission modulates some of the behavioral effects of haloperidol. Hence, the present study investigated the contribution of central histaminergic transmission in the cataleptic and neuroleptic effect of haloperidol respectively, using bar test and conditioned avoidance response (CAR) in a two-way shuttle box. The studies revealed that haloperidol (0.50 or 1 mg/kg, i.p.) exhibited cataleptic behavior and inhibited conditioned avoidance response (CAR) in the doses 0.25 or 0.50 mg in rats. The rats, pretreated centrally (i.c.v.) with histamine precursor, L-histidine (1, 2.5 μg) or histamine neuronal inducer ($H_3$ receptor antagonist), thioperamide (20, 50 μg/rat), showed an enhanced cataleptic effect with sub-maximal dose of haloperidol (0.5 mg/kg, i.p.). Similarly, the neuroleptic effect of haloperidol (0.25 mg/kg, i.p.) in CAR was also potentiated in the rats pretreated with L-histidine (2.5 μg) or thioperamide (50 μg/rat). Further, the cataleptic effect of haloperidol (1 mg/kg, i.p.) was attenuated in rats pretreated with the $H_1$ receptor antagonist, chlorpheniramine (60, 80 μg/rat, i.c.v.) or $H_2$ receptor antagonist, ranitidine (60 μg/rat, i.c.v.). However, the neuroleptic effect of haloperidol (0.5 mg/kg, i.p.) was completely reversed by pretreatment with ranitidine (60 μg/rat, i.c.v.), and partially attenuated by chlorpheniramine (80 μg/rat, i.c.v.). These findings suggest the possible involvement of histaminergic transmission in the cataleptic and neuroleptic effects of haloperidol probably via $H_1$ or $H_2$ receptor stimulation.



## 1. Introduction

Haloperidol is a typical antipsychotic agent belonging to a chemical class of butyrophenone. The neuroleptic and cataleptic effects of haloperidol are well ascribed to dopamine $D_2$ receptor blockade (Coppens et al., 1995; Mizuki et al., 1996; Rehavi et al., 2002; Seeman, 1987; Umathe et al., 2009; Wang et al., 2006).

An increasing body of evidence points towards the possible involvement of brain histaminergic system in the pathophysiology of schizophrenia as well as in the action of typical antipsychotic agents (Haas et al., 2008; Morisset et al., 2002; Pillot et al., 2002). However, the exact role of the central histaminergic system in psychosis is still unclear (Schwartz et al., 1995). Enhanced levels of tele-methyl histamine (t-MeHA), a major histamine metabolite are reported in the brain and cerebrospinal fluid of schizophrenic patients (Prell et al., 1995; Schwartz et al., 1971, 1991). In addition, a polymorphism within the histamine $H_2$ receptor gene has been linked with schizophrenia (Orange et al., 1996). Reduced histamine $H_1$ receptor-mediated response to histamine is often observed among psychotic patients (Nakai et al., 1991; Rauscher et al., 1980); and an overdose of first generation $H_1$ receptor antagonists is reported to produce toxic psychoses with hallucinations resembling schizophrenia (Morisset et al., 2002; Sangalli, 1997). These reports indicate a possible involvement of the central histaminergic system in psychosis.

It is well documented that dopamine is a cardinal neurotransmitter responsible for schizophrenic behavior. Incidentally, enhanced activity of histaminergic neurons is observed during hyperactivity of dopaminergic transmission (Pillot et al., 2002; Prell et al., 1995). Furthermore, stress-induced prolactin response is consequent to the inhibition of tuberoinfundibular dopaminergic neurons by $H_2$ receptor (Netti et al., 1988). Supportively, a report that histamine $H_3$ receptor controls the release of dopamine in striatum, suggest $H_3$ receptor expression on dopaminergic axons (Schlicker et al., 1994). In association with $D_2$ receptors, $H_3$ receptors are also shown to regulate striatal gene (Haas et al., 2008). In addition, histamine neuronal inducer i.e. $H_3$ receptor antagonist, thioperamide is reported to potentiate haloperidol-induced catalepsy (Akhtar et al., 2006; Pillot et al., 2002), whereas, $H_1$ receptor antagonists attenuate haloperidol-induced catalepsy on peripheral (i.p.) administration (Malec and Langwinski, 1983). These reports indicate the ability of the histaminergic system via histamine $H_1$, $H_2$ and $H_3$ to regulate the dopaminergic activity in the brain areas that are implicated in schizophrenia, and are also reported to be the target regions for the haloperidol-induced neuroleptic and extrapyramidal effect.

* Corresponding author at: Department of Pharmacology, Institute of Pharmaceutical Sciences, Guru Ghasidas University (A Central University), Koni, Bilaspur, Chhattisgarh 495009, India.
*E-mail address:* nishant.s.jain@hotmail.com (N.S. Jain).

http://dx.doi.org/10.1016/j.pbb.2015.10.004
0091-3057/

Thus, contemplating that histaminergic transmission might play a cardinal role in the haloperidol induced neuroleptic and cataleptic effect, the present investigation was carried out to determine the exact role of the central histaminergic transmission in the neuroleptic and cataleptic effect of haloperidol. Influence of histamine precursor, histaminergic $H_1$, $H_2$ or $H_3$ receptor antagonists was examined on the haloperidol induced cataleptic effect in bar test models and neuroleptic effects in the conditioned avoidance chamber in rats. The present investigation employed these models to study the neuroleptic or cataleptic effect of haloperidol and its modulation by histaminergic agents, as drug-induced catalepsy (freezing behaviors) is often evaluated to determine the potential of the antipsychotic agents to induced extra pyramidal syndrome (EPS) (Lieberman et al., 2006), and the conditioned avoidance chamber (shuttle box) is the most validated model for screening the antipsychotic drugs (Carlton, 1983; Clark et al., 1983; Davidson and Weidley, 1976; Wadenberg, 2010). The study revealed a contributory role of central histaminergic transmission in cataleptic and neuroleptic effect induced by haloperidol.

## 2. Materials and methods

### 2.1. Animals

Adult male Sprague–Dawley rats (220–250 g) were employed for the present investigation. The animals were housed (n = 2–3) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25 ± 2 °C, 55–65%). Rats received standard rodent chow (Goldmohar brand, Lipton India Ltd.) and water ad libitum. The animals were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise free room between 08:00 and 15:00 h. Separate groups (n = 6) of rats were used for each set of experiments. The animal studies were conducted after approval of experimental protocol by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals under Ministry of Environment and Forests, Government of India, New Delhi, India and all experiments were conducted in strict accordance with the guidelines for care and use of animals provided by the Committee for the Purpose of Control and Supervision of Experiments on animals (CPCSEA) is approved by the IAEC (994/a/GO/06/CPCSEA).

### 2.2. Drugs and administration

#### 2.2.1. Drugs and solutions

Histamine precursor, L-histidine and histamine neuronal inducer i.e. $H_3$ receptor antagonist, thioperamide were purchased from Sigma-Aldrich, USA. $H_1$ receptor antagonist, chlorpheniramine maleate and $H_2$ receptor antagonist, ranitidine hydrochloride were generously gifted by Zim Lab. Ltd., Nagpur, India. These drugs were dissolved in artificial cerebrospinal fluid (aCSF) of following composition; 0.2 M NaCl, 0.02 M $NaH_2CO_3$, 2 mM KCl, 0.5 mM $KH_2PO_4$, 1.2 mM $CaCl_2$, 1.8 mM $MgCl_2$, 0.5 mM $Na_2SO_4$, 5.8 mM D-glucose (dissolved in double distilled water) and injected through intracerebroventricular (i.c.v.) route via already fitted i.c.v. cannula. Haloperidol injections (brand name, Serenace) were purchased from RPG Life Sciences Ltd., Ankleshwar, India and it was diluted freshly in 0.9% saline and required dose was administered intraperitonially (i.p.). The doses of all the drugs were calculated as the free base. In the present study, the employed doses of histaminergic analogs were based on previous reports (Farzin et al., 2002; Hill et al., 1997) or preliminary data from our studies.

#### 2.2.2. Cannulation for intracerebroventricular (i.c.v.) injection

Rats were anesthetized with ketamine hydrochloride (50 mg/kg, i.p.) and xylazine (4 mg/kg, i.p.) injection and placed in stereotaxic instrument and stainless steel cannulae (Becton Dickinson, India, 24 gauge) were stereotaxically implanted with coordinates from Paxinos and Watson, 1998: AP −0.80 mm; ML +1.3 mm and DV +3.5 mm; related to bregma. A guide cannula was secured to the skull using mounting screws and dental cement (Dental Products of India, Mumbai). A stainless steel dummy cannula was used to occlude the guide cannula when not in use. The animals were then allowed to recover for a week under antimicrobial cover of cefotaxim (50 mg/kg/day, s.c.), during which they were also habituated to the i.c.v. injection procedure to minimize nonspecific stress induced changes in traits. Injections were made using a Hamilton microliter syringe (Hamilton, Nevada, USA) connected to an internal cannula (31 gauges) by polyethylene tubing with a volume of 5.0 μl was administered over a period of 1 min into the right lateral ventricle. The injection cannula was left in place for a further 1 min before being slowly withdrawn to avoid back flow. At the end of all i.c.v. experiments, a dilute India ink was injected (5.0 μl) and the animals were euthanized by pentobarbitone overdose. Only data from animals showing uniform distribution of ink into lateral ventricles were used for statistical analysis.

### 2.3. Behavioral tests

#### 2.3.1. Catalepsy

Catalepsy is defined as the long term maintenance of an animal in an externally imposed abnormal posture. The severity of catalepsy in individual rat was assessed using the bar test. The apparatus consists of a wooden bar of 0.8 cm in diameter placed at a height of 9.0 cm above the tabletop. It was determined by gently placing the forepaws of the rat over a 0.8 cm diameter wooden bar, fixed horizontally at a height of 9.0 cm above the tabletop. The time required in seconds (sec) to bring both the forepaws down by rat to the tabletop was recorded, with maximum cut off time of 300 s. The catalepsy was recorded at 30, 60, 90, 120, 150, and 180 min after the administration of the drug. The catalepsy test was performed in a sound attenuated chamber with low, indirect incandescent lighting (about 20 lx). In order to normalize the data, duration of catalepsy obtained in seconds was converted into natural logarithms (ln). The behavior of the rat was video recorded by a camera placed 2 m parallel to the horizontal table. A trained experimenter blind to the given treatments, analyzed the video recordings (Umathe et al., 2009).

#### 2.3.2. Conditioned avoidance response (CAR)

The conditioned avoidance response was performed according to the procedure described earlier (Umathe et al., 2009). The conditioning experiments were carried out in a two-way shuttle box, composed of two stainless steel modular testing units equipped with an 18 bar insulated shock grid floor and buzzer. Electric shocks were provided to the grid floor by a master shock supply. The experiments were carried out in a sound attenuated chamber with low, indirect incandescent lighting (about 20 lx). Rats were trained individually to move from one compartment of a shuttle box into other upon presentation of the 10 s buzzer tone (conditioned stimulus). If the rat failed to respond, the tone was further conditioned with an unconditioned stimulus in the form of an electric shock (0.5 mA), delivered to the grid floor of the chamber for a period of 10 s. Each animal was subjected to a daily session of 10 trials separated by 20 s inter-trial interval. The trial was terminated once the rat has moved into the other compartment during the conditioned stimulus and unconditioned stimulus period. Crossings made during the conditioned stimulus period were recorded as avoidance response and those made during unconditioned stimulus were recorded as escape response. All animals were trained for a week. Only those animals characterized by a high level of avoidance responding (>90%) were used for further experiments. A separate group of trained rats (n = 6 per group) was employed for individual dose effect of the drugs. After treatment, rats were placed individually in the shuttle box for the standard 10 trial session of CAR. The results were expressed as the number of trials avoided. The observations were made by a trained experimenter who was unaware of the treatments given.