European Journal of Pharmacology 830 (2018) 26–32

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Behavioural pharmacology

Lack of dopamine supersensitivity in rats after chronic administration of blonanserin: Comparison with haloperidol

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ARTICLE INFO

Keywords:
Dopamine supersensitivity
Dopamine D_2 receptor
Dopamine D_3 receptor
Locomotor activity
Haloperidol
Blonanserin

ABSTRACT

Long-term treatment with antipsychotic drugs in patients with schizophrenia can lead to dopamine supersensitivity psychosis. It is reported that repeated administration of haloperidol caused dopamine supersensitivity in rats. Blonanserin is an atypical antipsychotic drug with high affinity for dopamine D_2, D_3 and serotonin$_{2A}$ receptors. In this study, we investigated whether chronic administration of blonanserin leads to dopamine supersensitivity. Following oral treatment with blonanserin (0.78 mg/kg) or haloperidol (1.1 mg/kg) twice daily for 28 days, the dopamine D_2 agonist quinpirole-induced hyperlocomotion test and a dopamine D_2 receptor binding assay were conducted. We found that haloperidol significantly enhanced both quinpirole-induced hyperlocomotion and striatal dopamine D_2 receptor density in rats. On the other hand, repeated administration of blonanserin had no effect on either locomotor activity or striatal dopamine D_2 receptor density. Further, our results show that mRNA levels of dopamine D_2 and D_3 receptors in several brain regions were unaffected by repeated administration of both agents. In addition, we examined the effect of the dopamine D_3 receptor antagonist PG-01037 on development of dopamine supersensitivity induced by chronic haloperidol treatment and showed that PG-01037 prevents the development of supersensitivity to quinpirole in chronic haloperidol-treated rats. Given the higher affinity of blonanserin at dopamine D_3 receptors than haloperidol, antagonism of blonanserin at dopamine D_3 receptors may play a role in lack of dopamine supersensitivity after chronic administration. The present findings suggest long-term treatment with antipsychotic dose of blonanserin may be unlikely to lead to dopamine supersensitivity.

1. Introduction

Antipsychotics that act as dopamine D_2 receptor antagonists are the most commonly prescribed drugs for schizophrenia and are known to exert sufficient therapeutic effect on acute symptoms of schizophrenia. However, chronic treatment with dopamine D_2 receptor antagonists can induce dopamine supersensitivity psychosis (DSP) in patients with schizophrenia (Chouinard, 1991; Chouinard et al., 1988). DSP is characterized by acute exacerbation of psychotic symptoms following treatment dose reduction or discontinuation, relapse after minor stress, tolerance to previously observed therapeutic effects, and co-occurring tardive dyskinesia (Iyo et al., 2013; Seeman and Seeman, 2014). Although the exact pathogenic mechanism of DSP is still unclear, it is considered that DSP is closely associated with compensatory up-regulation of dopamine D_2 receptors following prolonged and excessive blockade of this receptor (Samaha et al., 2008, 2007).

Blonanserin is an atypical antipsychotic with high affinity for the dopamine D_{2L} receptor (K_i; 0.284 nM), dopamine D_3 receptor (K_i; 0.277 nM) and serotonin$_{2A}$ (5-HT_{2A}) receptor (K_i; 0.640 nM) (Baba et al., 2015; Murasaki et al., 2008). BNS is approved for the treatment of schizophrenia in Japan, South Korea and China (Deeks and Keating, 2010; Li et al., 2015). Compared to haloperidol, blonanserin has superior clinical efficacy on schizophrenia negative symptoms with lower risk of akathisia (Kishi et al., 2013). Besides, various studies in animal models of schizophrenia symptoms suggest that blonanserin can ameliorate both positive and negative symptoms, including cognitive impairment associated with schizophrenia (Kotani et al., 2016; Nagai et al., 2003; Oka et al., 1993). Interestingly, although blonanserin binding affinity for the dopamine D_2 receptor is higher than that of haloperidol (Murasaki et al., 2008), blonanserin is reported to exhibit

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https://doi.org/10.1016/j.ejphar.2018.04.014
Received 20 November 2017; Received in revised form 5 April 2018; Accepted 13 April 2018
Available online 22 April 2018

lower risk of catalepsy in rodents (Oka et al., 1993). Furthermore, in our previous study using a possible animal model of tardive dyskinesia, chronic administration of blonanserin, unlike haloperidol, had no effect on SKF38393 (a dopamine D_1 receptor agonist)-induced oral activity enhancement, suggesting that chronic treatment with blonanserin does not induce tardive dyskinesia-like symptoms, which often co-occur with dopamine supersensitivity (Noda et al., 1993).

In order to further elucidate the difference between blonanserin and haloperidol in the development of dopamine supersensitivity, we conducted the dopamine D_2 agonist quinpirole-induced hyperlocomotion test and a striatal dopamine D_2 receptor binding assay in rats following repeated administration of blonanserin or haloperidol. In addition, we determined mRNA levels of dopamine D_2 and D_3 receptors in several brain regions of these experimental rats. Blonanserin exhibited almost equal affinities for dopamine D_2 and D_3 receptors (D_2/D_3 K_i ratio, 1.025) (Baba et al., 2015), while haloperidol had higher affinity for dopamine D_2 receptors than D_3 receptors (D_{2L} K_i, 2.34 nM; D_3 K_i, 12 nM; D_2/D_3 K_i ratio, 0.195) (Richtand et al., 2007). Hence, development of dopamine supersensitivity may be suppressed if affinity of haloperidol for D_3 receptors is higher than the actual affinity. To investigate this, we used the quinpirole-induced hyperlocomotion test following continuous co-administration of haloperidol and a dopamine D_3 receptor antagonist.

2. Materials and methods

2.1. Animals

Male Wistar rats were purchased from CLEA Japan, Inc. (Japan). The animals were housed in plastic cages (4 rats/cage) maintained in a temperature (23 ± 3 °C)- and humidity (55 ± 15%)-controlled animal room under a 12/12 h light/dark cycle (light on at 07:00). The animals had free access to food and water and were acclimatized for at least seven days before the initiation of test-drugs administration. Altered dopaminergic systems in rat brain during adolescence are reported (Spear, 2000). In our present study, the repeated or continuous administration of drugs were started during mid-adolescence. All experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee of Sumitomo Dainippon Pharma Co., Ltd.

2.2. Drugs

Haloperidol, blonanserin and methamphetamine were synthesized in Sumitomo Dainippon Pharma Co., Ltd (Osaka, Japan). (-)-Quinpirole hydrochloride and PG-01037 dihydrochloride were purchased from Tocris Bioscience (Bristol, UK). [^{3}H]Raclopride (76.0 Ci/mmol) was purchased from PerkinElmer Japan (Yokohama, Japan). Other chemicals were purchased commercially. Blonanserin and haloperidol were suspended in 0.5% methylcellulose (MC), which served as vehicle for oral administration. Haloperidol and PG-01037 were dissolved in 2% glacial acetic acid/H_2O solution (pH adjusted to 3.6 with NaOH) containing 0.5% Tween 80 for continuous Alzet osmotic minipump (model 2ML2; DURECT corp., USA) administration. Methamphetamine and quinpirole were dissolved in physiological saline.

2.3. Methamphetamine-induced hyperlocomotion test

Methamphetamine-induced hyperlocomotion test was performed to determine haloperidol and blonanserin ED_{50} values for induction of antipsychotic-like effect in rats. Rats (8 weeks old) were orally given vehicle, haloperidol (0.1–3 mg/kg) or blonanserin (0.1–3 mg/kg) 60 min before subcutaneously injection of methamphetamine (1 mg/kg). The rats were then individually placed in a top-opened plastic box (438 × 438 × 295 mm), and locomotor activity was measured for 60 min using an automated system (SCANET MV-40) (Melquest Ltd., Toyama, Japan).

2.4. Oral drug administration and tissue collection

Animals (6 weeks old) were assigned to three groups, i.e. vehicle-treated group, haloperidol-treated group and blonanserin-treated group. They were then orally administered haloperidol (1.1 mg/kg), blonanserin (0.78 mg/kg) or vehicle twice daily (between 8:00 and 9:00 and between 18:00 and 19:00) for 28 days in a dosing volume of 5 ml/kg. The doses of haloperidol and blonanserin were determined, based on the results of methamphetamine-induced hyperlocomotion test, as twice the ED_{50} of each drug antipsychotic-like effect in rats. Seven days after the last administration, the animals were used in a quinpirole-induced hyperlocomotion test or decapitated to collect the striatum for radioligand binding assay. The obtained striatum samples were frozen in dry ice powder and stored at − 80 °C until use. For mRNA quantification experiment, the animals (6 weeks old) were given each drug twice daily for 28 days and decapitated 4 h after morning administration of haloperidol, blonanserin, or vehicle on Day 29. Their brains were quickly dissected into 5 regions: prefrontal cortex, striatum, nucleus accumbens, hippocampus and cerebellar lobes 9 and 10 (L9/10). The obtained brain samples were stored in RNAlater solution at − 20 °C until use. Animals decapitation time (i.e. 4 h after test drugs last administration) was chosen based on a report showing that repeated administration of haloperidol alter dopamine receptor mRNA (D'Souza et al., 1997).

2.5. Continuous osmotic minipump administration

Animals (7 weeks old) were assigned to four groups, i.e. vehicle-treated group, haloperidol-treated group, PG-01037-treated group, and HPD plus PG-treated group. An Alzet osmotic minipump containing either vehicle (2% glacial acetic acid/H_2O solution), haloperidol (0.75 mg/kg/day), PG-01037 (0.6 mg/kg/day) or haloperidol plus PG-01037 was then implanted into each animal under isoflurane inhalational anesthesia. Briefly, a 1.5 cm-wide incision was made in each animal's lower back, and forceps were used to loosen the connective tissue between the scapulae. The minipump was inserted to lie on the right side of the scapula with its flow moderator pointed away from the incision. The incision was then closed using 9 mm surgical staples and treated with antibiotics. All minipumps were removed 14 days after implantation, and the animals were used for quinpirole-induced hyperlocomotion test 7 days after minipumps extraction. The doses of haloperidol and PG-01037 were selected based on the results of our previous report (Oda et al., 2015) and on those of our preliminary experiments, respectively.

2.6. Quinpirole-induced hyperlocomotion test

Seven days after repeated oral administration or continuous osmotic minipump administration, the rats were individually put in a top-opened plastic box (438 × 438 × 295 mm) and habituated for 60 min. After habituation, each rat was subcutaneously injected with quinpirole (0.5 mg/kg) and immediately returned to the box. Locomotor activity was measured using an automated system (SCANET MV-40) (Melquest Ltd., Toyama, Japan) every 10 min starting 30 min before quinpirole injection until 60 min after quinpirole injection. The dose of quinpirole was selected based on information in the literature (Lau et al., 2003).

2.7. Radioligand binding assay

The radioligand binding assay for striatal dopamine D_2 receptors was performed as described in our previous report (Oda et al., 2015). Briefly, each frozen striatal sample was homogenized in 50 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl (assay buffer) and then centrifuged at 40,000 ×g for 15 min