Neuroscience Letters 549 (2013) 97–102

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

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

Effect of blonanserin on methamphetamine-induced disruption of latent inhibition and c-Fos expression in rats

Aki Kuramashi[a], Hiroshi Abe[a,*], Go Koganemaru[a], Hisae Matsuo[a], Tetsuya Ikeda[b], Kosuke Ebihara[a], Hideki Funahashi[a], Ryuichiro Takeda[a], Toshikazu Nishimori[b], Yasushi Ishida[a]

[a] Department of Psychiatry, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki-city, Miyazaki 889-1692, Japan
[b] Division of Neurobiology, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki-city, Miyazaki 889-1692, Japan

HIGHLIGHTS

- We examined the pharmacological profile of blonanserin, a novel antipsychotic.
- Blonanserin ameliorates methamphetamine-induced disruption of latent inhibition.
- Blonanserin increases c-Fos expression in the shell area of the nucleus accumbens.

ARTICLE INFO

Article history:
Received 22 March 2013
Received in revised form 3 June 2013
Accepted 13 June 2013

Keywords:
Blonanserin
Haloperidol
Latent inhibition
Immediate-early gene protein
Schizophrenia

ABSTRACT

To clarify the psychopharmacological profile of blonanserin, a novel antipsychotic, we examined its effect on the methamphetamine-induced disruption of latent inhibition (LI) and the neural activation related to this effect in rats. To evaluate the LI, we used a conditioned emotional response in which a tone (conditioned stimulus) was paired with a mild foot shock (unconditioned stimulus). This paradigm was presented to rats licking water. Methamphetamine-induced (1.0 mg/kg, i.p.) disruption of LI was significantly improved by the administration of a higher dose (3.0 mg/kg, i.p.) of blonanserin and tended to be improved by 1.0-mg/kg blonanserin and 0.2-mg/kg haloperidol but not by a lower dose (0.3 mg/kg) of blonanserin. Immunohistochemical examination showed blonanserin (3.0 mg/kg, i.p.) increased c-Fos expression in the shell area but not in the core area of the nucleus accumbens while methamphetamine (3.0 mg/kg, i.p.) produced the opposite expression pattern. Blonanserin also increased the number of c-Fos expressions in the central amygdala nucleus but not in the basolateral amygdala nucleus or the prefrontal cortex. Blonanserin ameliorates the methamphetamine-induced disruption of LI, as other antipsychotics do, and a neuronal activation and/or modulation of neurotransmission in the nucleus accumbens is related to the disruption of LI by methamphetamine and to its amelioration by blonanserin.

1. Introduction

The latent inhibition (LI) effect is the suppression of performance on a classical conditioning task when a conditioned stimulus (CS) is pre-exposed before conditioning [8]. That is, if a CS is presented several times without an unconditioned stimulus (US), the person or animal learns to ignore, or not to pay attention to, the stimulus, and, consequently, the strength of the subsequent conditioning is inhibited [23]. The disruption of LI has been observed in patients with schizophrenia and in healthy humans and rats under dopamine releaser treatment [22] and is considered to be related to the functional decline in attentional filtering, a cognitive deficit observed in schizophrenia [23]. Typical and atypical antipsychotics, which mainly block dopamine receptors, ameliorate the disrupted LI and even enhance LI [3,5,9,16,17,25,26]. Therefore, we can estimate the potential antipsychotic profiles, especially for cognitive deficits, of novel compounds by examining their effects on LI.

Blonanserin, 2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta [b] pyridine, is a novel atypical antipsychotic that has a binding profile different from that of other atypical antipsychotics: it has high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors and weak affinity for D_1, 5-HT_{1A}, 5-HT_6, 5-HT_7, histamine H_1, and muscarinic M_1 receptors and

* Corresponding author. Tel.: +81 985 85 2969; fax: +81 985 85 5475.
E-mail addresses: m11072@fc.miyazaki-u.ac.jp (A. Kuramashi), abehiro@med.miyazaki-u.ac.jp (H. Abe), g-maru@fc.miyazaki-u.ac.jp (G. Koganemaru), hisam56@fc.miyazaki-u.ac.jp (H. Matsuo), ikedat@fc.miyazaki-u.ac.jp (T. Ikeda), ko/ebi@fc.miyazaki-u.ac.jp (K. Ebihara), funapi@fc.miyazaki-u.ac.jp (H. Funahashi), psytr@fc.miyazaki-u.ac.jp (R. Takeda), ntoshi@med.miyazaki-u.ac.jp (T. Nishimori), ishiday@fc.miyazaki-u.ac.jp (Y. Ishida).

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.06.020

for α_1, α_{2c}, and β adrenoceptors [11,14]. Blonanserin has the highest affinity for D_2 receptors, and its affinity is the highest among all antipsychotics [11]. Clinically, blonanserin exhibits atypical antipsychotic properties with efficacy against positive and negative symptoms of schizophrenia [4,7]; however, the effects of blonanserin on cognitive deficits in schizophrenia have not been fully examined. Basic research with rodents showed that amphetamine-induced disruption of pre-pulse inhibition (PPI) [20] and phencyclidine-induced impairment in a novel object recognition test [6] were relieved by blonanserin. That is, there are only two reports on the potential ameliorating effect and mechanism of blonanserin of the cognitive deficits in schizophrenic model animals. To examine the remedial effects of blonanserin on disrupted LI and its underling neurobiological mechanisms, we conducted behavioral and morphological studies focusing on the brain areas potentially related to LI.

2. Materials and methods

2.1. Animals

We used 157 adult male Sprague–Dawley rats (Charles River Laboratories, Japan), weighing 250–330 g. They were housed in a temperature-controlled colony room in separate cages at 23 ± 1 °C with 50 ± 10% relative humidity on a 12:12-h light: dark cycle (lights on from 08:00 to 20:00 h). Water access was restricted, as described below, and food access was unrestricted. The experimental procedures were performed in strict adherence with the guidelines of the University of Miyazaki for the care and use of experimental animals and with the approval of the ethical committee for animal experimentation at the University of Miyazaki.

2.2. LI evaluation

We used 93 rats in a behavioral experiment designed to evaluate LI. LI was assessed using an off-baseline conditioned emotional response procedure in rats licking water. The test chamber was 24.0 cm long, 29.0 cm wide, and 25.0 cm high (Ohara Ika Sangyo, Tokyo, Japan) with a retractable water bottle and a speaker. The chamber was placed in a soundproof box. Licks were detected with a drinkometer (Ohara Ika), and the data were captured using a program written in LabVIEW (National Instruments Co., Tokyo, Japan).

In an initial training procedure (days 1–9), the rats (after being handled for 5 min) were placed one by one in the test chamber for 5 min on four consecutive days. For the next five consecutive days, they were water restricted overnight and then placed in the chamber and allowed to take water freely for 15 min by licking the tip of the water bottle. The rats were given free access to water for 1 h after the training procedure, at which time the water was again removed.

The LI indexing procedure was conducted on days 10–13 and consisted of four sessions, with a 24-h break between them. (1) In a pre-exposure session, one group of rats (the pre-exposed (PE) group) were placed one at a time in the chamber and received 20 tone presentations (2.8 kHz, 90 dB, 10 s) with an inter-stimulus interval of 50 s without the water bottle. The remaining rats (the non-pre-exposed (NPE) group) were likewise placed in the chamber for the same period of time without being exposed to the tone. (2) In a conditioning session, all the rats were placed one at a time in the chamber without the water bottle, and a CS (tone, 2.8 kHz, 90 dB, 10 s) was presented, immediately followed by an US (0.5 mA, 1.0 s, foot shock via floor grid). The first stimulus pairing was administered 5 min after the start of the session, and the pairings were given 5 times with an inter-pairing interval of 5 min. (3) In a retraining session, all the rats were placed one at a time in the chamber and took water freely for 15 min by licking the tip of the water bottle, as in the initial training. (4) In a test session, all the rats were placed one at a time in the chamber and took water freely from the tip of the water bottle. When the number of licks reached 300, the CS was continuously presented until 600 licks had been taken. The times taken to take licks 150–250 (period *A*) and 302–402 (period *B*) were measured. The suppression ratio was defined as $B/(A+B)$.

2.3. Drug treatment in LI evaluation

All drug treatments were conducted before the conditioning session, and the effects of 0.2-mg/kg haloperidol (Hal 0.2) and 0.3-, 1.0-, and 3.0-mg/kg blonanserin (BNS 0.3, BNS 1.0, and BNS 3.0) on methamphetamine-induced (1.0 mg/kg) disruption of LI were examined. The drug dosages were determined by reference to previous studies that examined the effects of intraperitoneal injection of antipsychotics on LI [3,9,25,26]. Sixty-nine rats were randomly assigned to ten experimental groups in a 2×5 factorial design with main factors of pre-exposure (NPE, PE) and drug (saline (SAL), Hal 0.2, BNS 0.3, BNS 1.0, and BNS 3.0). Blonanserin (Dainippon Sumitomo Pharma. Co., Ltd., Japan) was suspended in and diluted with an appropriate amount of 0.5% tragacanth (Sigma Aldrich, Co., Ltd., USA) to make 0.3-, 1.0-, and 3.0-mg/mL blonanserin solutions. Haloperidol and methamphetamine (Dainippon Sumitomo Pharma. Co., Ltd., Japan) were diluted with appropriate amounts of saline to make 0.2- and 1.0-mg/mL solutions, respectively. The rats were injected intraperitoneally with a 1.0-mL/kg antipsychotic (or saline for the control group), and methamphetamine was injected intraperitoneally 75 min after the injection of the antipsychotic and 15 min before the conditioning session. The timings of the methamphetamine and antipsychotics treatments were determined by referring to a previous report [26] and to one stating that dopamine release reaches a maximum level 90–120 min after the treatment of blonanserin [13]. To obtain a standard suppression ratio, we prepared PE and NPE group rats (naïve) without any drug treatment ($n = 12$ for each).

2.4. c-Fos evaluation

An immunohistochemical experiment was used to examine the patterns of c-Fos immunopositive cells in the prefrontal cortex (PFC), accumbens core area (AcbC), accumbens shell area (AcbSh), central amygdala nucleus (Ce), and basolateral amygdala area (BLA) after the injection of an antipsychotic and/or methamphetamine. Sixty-four rats were randomly assigned to nine experimental groups in a 3×3 factorial design with main factors of antipsychotics (vehicle (Veh), 0.2-mg/kg haloperidol (Hal 0.2), or 3.0-mg/kg blonanserin (BNS 3.0)) and methamphetamine (SAL, 1.0-mg/kg methamphetamine (MAP 1.0), or 3.0-mg/kg methamphetamine (MAP 3.0)). All drugs were diluted in the same manner as in the behavioral experiment. The Veh group was treated with 0.5% tragacanth.

Following handling of the rats for 5 min over 4 days, an antipsychotic (or Veh) was intraperitoneally administrated. Methamphetamine (or SAL) was injected intraperitoneally 75 min later and 120 min before perfusion. Our timing of the methamphetamine treatment is based on a finding that c-Fos expressions are detected 15–120 min after methamphetamine treatment [19]. The rats were then deeply anesthetized with sodium pentobarbital and perfused transcardially with saline followed by 4% paraformaldehyde in 0.1-M phosphate buffer (PB; pH 7.4). Their brains were removed immediately and postfixed at 4 °C for 1 h in the above fixative. After fixation, the samples were immersed

in 0.1-M PB with 10% sucrose at 4 °C for 1 h and then cryoprotected at 4 °C overnight in the same buffer with 30% sucrose. The samples were subsequently cut on a freezing microtome into 50-μm coronal sections for immunohistochemistry. Sections through the PFC, AcbC, AcbSh (1.70 mm rostral to the bregma), Ce, and BLA (2.80 mm caudal to the bregma) were selected for histological study [15]. The antibody for c-Fos (1:5000) was rabbit polyclonal antisera (sc-52; Santa Cruz Biotechnology, CA, USA). Biotinylated secondary antibodies were coupled with streptavidin-biotinylated horseradish peroxidase, and the reaction was visualized using diaminobenzidine as a chromogen enhanced by cobalt chloride in accordance with the manufacturer's instructions on the use of a streptavidin-biotin system (Histofine SAB-PO(R) kit, Nichirei, Tokyo, Japan). Between each incubation step, the free-floating sections were thoroughly rinsed with phosphate-buffered saline. c-Fos immunoreactivity was analyzed using light microscopy. Four sections were taken through each structure of each animal. They were taken at the same level along the animal's anteroposterior axis to avoid variance of the level of the structure among animals. The expression of c-Fos was quantified by counting the number of cells immunopositive for c-Fos in 0.25 × 0.25 mm squares using a 20× microscope objective. The c-Fos immunopositive cells were counted bilaterally and averaged per structure/animal.

3. Results

3.1. Effect of blonanserin on methamphetamine-induced disruption of LI

The naïve PE group showed a significantly lower suppression ratio than the naïve NPE group (t-test, $p < .05$), demonstrating that the settings of the three parameters used (the number of tone pre-exposures, the number of pairings, and the strength of the foot shock) were sufficient for creating LI in naïve rats. Fig. 1 shows the mean suppression ratios for the PE and NPE groups for the five drug conditions. Two-way ANOVA with main factors of pre-exposure (NPE, PE) and drug (SAL, Hal 0.2, BNS 0.3, BNS 1.0, BNS 3.0) carried out on the suppression ratios yielded a significant interaction of pre-exposure × drug [$F(4, 59) = 2.76$, $p < .05$]. The simple main effect of pre-exposure was significant for PE [$F(4, 59) = 5.95$, $p < .001$] but not for NPE. For PE, post hoc Bonferroni tests revealed that the suppression ratios for BNS 3.0 were significantly lower than those for SAL and BNS 0.3 ($p < .00001$, $p < .005$, respectively). In addition, the simple main effects of drug were significant for BNS 3.0 [$F(1, 59) = 25.60$, $p < .001$] and tended to be significant for Hal 0.2 and BNS 1.0 [$F(1, 59) = 3.73$, $p < .1$, $F(1, 59) = 3.16$, $p < .1$, respectively].

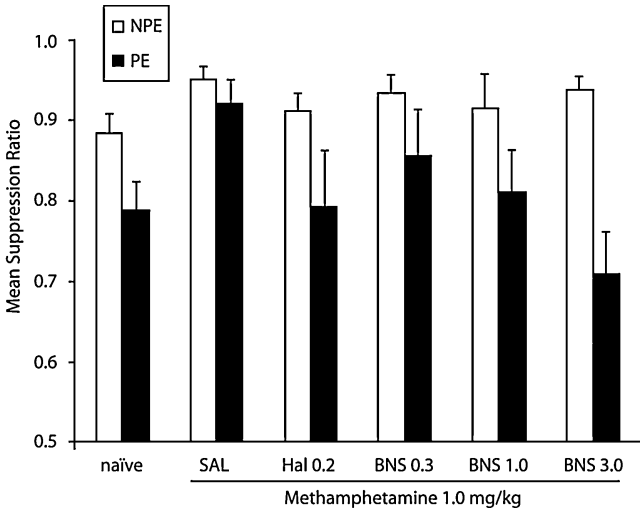

Fig. 1. Mean and standard error of suppression ratio for non-pre-exposed (NPE) and pre-exposed (PE) groups under naïve and five drug conditions: saline (SAL), 0.2-mg/kg haloperidol (Hal 0.2), 0.3-, 1.0- and 3.0-mg/kg blonanserin (BNS 0.3, 1.0, 3.0). The suppression ratio was defined as $B/(A+B)$: A is the time taken for 150–250 licks before conditioned stimulus exposure. B is the time taken for 302–402 licks after conditioned stimulus exposure.

3.2. c-Fos expression after methamphetamine and/or antipsychotic administration

The number of c-Fos immunopositive cells counted for the PFC, AcbC, AcbSh, Ce, and BLA sections for all 64 animals in the Veh, Hal 0.2, and BNS 3.0 groups, which were pretreated, 75 min beforehand, with SAL, MAP 1.0, and MAP 3.0, respectively, was used for statistical analysis (Figs. 2 and 3). Two-way ANOVA with main factors of antipsychotic (Veh, Hal 0.2, BNS 3.0) and methamphetamine (SAL, MAP 1.0, MAP 3.0) was carried out for each brain region, and simple main effect examination and post hoc Bonferroni testing were conducted as needed. For the PFC and AcbC sections, the main effects of methamphetamine were significant [$F(2, 54) = 4.64$ for PFC and $F(2, 53) = 6.45$ for AcbC, $p < .05$ for both] while the other effects were not. Post hoc Bonferroni testing revealed that the number of cells in the MAP 3.0 samples was significantly greater than that in the SAL samples ($p < .005$ for the PFC, $p < .01$ for the AcbC). For the AcbSh section, the main effect of the antipsychotic was significant [$F(2, 54) = 4.49$, $p < .05$] while the other effects were not. Post hoc Bonferroni testing revealed that the number of cells in the BNS 3.0 samples was significantly greater than that in the Veh samples ($p < .01$). For the Ce section, significant interaction between the antipsychotic and methamphetamine was detected [$F(4, 55) = 4.10$, $p < .01$]. The simple main effect on methamphetamine was significant for MAP 3.0 [$F(2, 55) = 14.53$, $p < .001$], and post hoc Bonferroni testing for MAP 3.0 revealed that the number of cells in the BNS 3.0 samples was significantly greater than those in the Veh and Hal 0.2 samples ($p < .001$ and $p < .0001$, respectively). On the other hand, the simple main effect on the antipsychotic was significant for Veh [$F(2, 55) = 4.23$, $p < .05$] and BNS 3.0 [$F(2, 55) = 21.53$, $p < .001$], and the post hoc Bonferroni test for Veh revealed that the number of cells in the MAP 3.0 samples was significantly greater than that in the SAL ones ($p < .01$). For BNS 3.0, the numbers of cells in the MAP 3.0 samples was significantly greater than those in the SAL and MAP 1.0 ones ($p < .001$ for both). There were no significant differences in the BLA sections.

4. Discussion

These results show that the disruption of LI induced by methamphetamine (1.0 mg/kg) is significantly ameliorated by administration of 3.0-mg/kg blonanserin and tends to be ameliorated by 0.2-mg/kg haloperidol and 1.0-mg/kg blonanserin, but not by 0.3-mg/kg blonanserin.

The disrupted LI caused by dopamine release by amphetamine and methamphetamine, is ameliorated by various typical and atypical antipsychotics, including olanzapine [5], chlorpromazine [17], haloperidol [21], clozapine [26], risperidone [25], and aripiprazole [9].

Blonanserin is a novel atypical antipsychotic that has been commercialized in Japan and Korea [1] and has been demonstrated to be effective in treating schizophrenia [4,7]. In the present study, the highest dose (3.0 mg/kg) of blonanserin remedied disrupted LI caused by methamphetamine treatment. It has been suggested that antagonistic action against the D_2 receptor is of critical

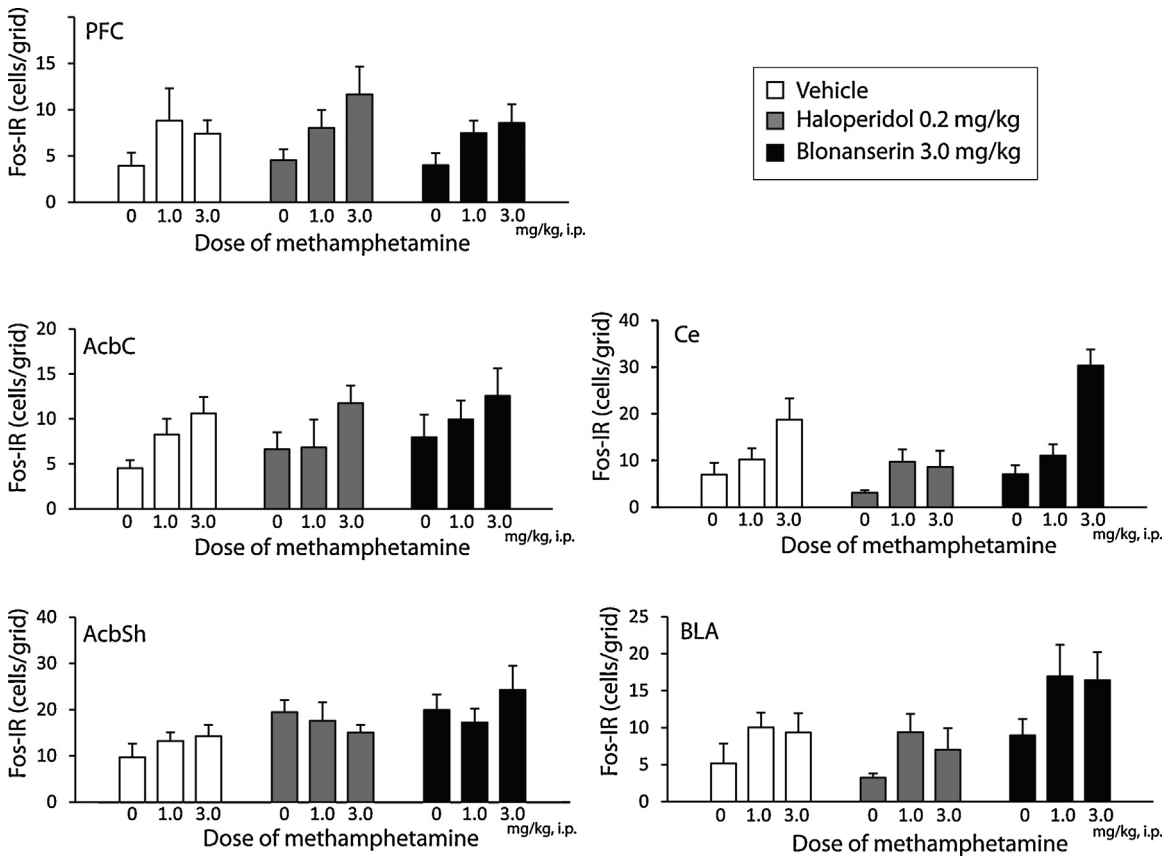

Fig. 2. Effect of blonanserin, haloperidol, vehicle, and methamphetamine on c-Fos expression. Bars represent mean, and error bars represent standard error. The treatment of methamphetamine significantly increased the number of c-Fos immunoreactive (Fos-IR) cells in prefrontal cortex (PFC) and accumbens core area (AcbC). In accumbens shell area (AcbSh), the treatment of 3.0-mg/kg blonanserin significantly increased the number of Fos-IR cells. In the central amygdala nucleus (Ce), methamphetamine treatment significantly increased Fos-IR neurons in vehicle and 3.0-mg/kg blonanserin exposed groups. Significant differences were not detected in the basolateral amygdala nucleus (BLA).

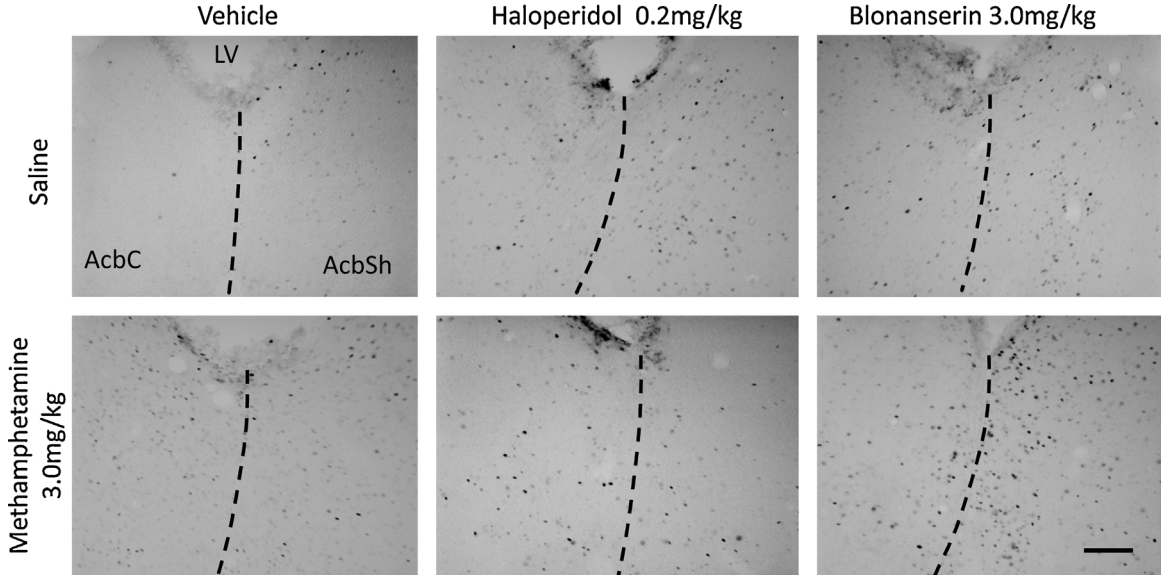

Fig. 3. Bright-field photomicrographs showing the enhancement of Fos-IR cells in the accumbens core area (AcbC) and shell area (AcbSh) of the vehicle (Veh), 0.2-mg/kg haloperidol (Hal 0.2), and 3.0-mg/kg blonanserin (BNS 3.0) treatment groups, which were pretreated with saline (SAL) and 3.0-mg/kg methamphetamine (MAP 3.0), respectively. MAP 3.0 significantly increased Fos-IR cells in AcbC more than SAL in the Veh, Hal 0.2, BNS 3.0 groups. On the other hand, there were significantly more Fos-IR cells in the AcbSh of the BNS 3.0 group than that of the Veh group with both SAL and MAP 3.0 treatments. The dotted lines demarcate the border between AcbC and AcbSh. LV: lateral ventricle. Scale bar = 100 μm.

importance to the remedial effect on disrupted LI [23]. Blonanserin has high affinities for the D_2 receptor (Ki = 0.284 nM) and the 5-HT_{2A} receptor (Ki = 0.64 nM), and the strength of D_2 receptor binding in blonanserin is stronger than in haloperidol (Ki = 3.19 nM) [11]. Because the blockade of 5-HT receptors during the conditioning phase in the LI procedure does not affect LI [25], strong D_2 receptor blockade action of blonanserin might have ameliorated the disrupted LI in the present study, in which only 0.2-mg/kg haloperidol showed a significant amelioration tendency ($p = .0581$). However, further studies are needed to determine whether the ameliorating effect of blonanserin in the present study is due to the strong affinity for the D_2 receptor, the comparatively high concentration (3.0 mg/kg) of blonanserin, or both. In any case, this is the first report that blonanserin has an ameliorating effect on disrupted LI, as other antipsychotics have.

Immunohistochemical examination showed that the patterns of c-Fos expression in the AcbSh and AcbC were affected differently by treatments of methamphetamine and blonanserin. The nucleus accumbens (NAc) and its connections with the prefrontal cortex, hippocampus, basolateral amygdala area, and entorhinal cortex are thought to play principal roles in the regulation of LI [23]. Especially in the NAc, there are two functionally different sub regions, AcbSh and AcbC, and the lesion of AcbSh disrupts LI while the same treatment of AcbC does not LI [16,18,24]. "Switching models" in LI has been suggested to explain this functional differentiation, in which AcbC facilitates CS-reinforcement contingencies during conditioning while AcbSh suppresses them [23]. The elevated neuronal activation in the AcbC, but not in the AcbSh, and the disrupted LI after methamphetamine treatment in the present study fit with this model well.

Antagonizing the D_2 receptors by treatment of haloperidol within the AcbSh enhances LI [12]. A potential explanation is the reduction in the dopamine function in the AcbSh, which enhances glutamatergic inputs from the prefrontal cortex, hippocampus, and amygdala, because dopamine suppresses glutamatergic inputs in AcbSh via D_2 receptors on their terminals [10]. Blonanserin could also strongly antagonize the D_2 receptors and might enhance and revive glutamatergic inputs in the AcbSh, which are suppressed by methamphetamine treatment. This process is reflected in higher c-Fos expression in this area and is related to the remedial effect of blonanserin in the present behavioral experiment. Because the blonanserin treatment did not affect the number of c-Fos expressions in the AcbC, the disruption of LI by methamphetamine or its amelioration by blonanserin in the behavioral experiment would result in doubly dissociated patterns of c-Fos expression in the AcbSh and AcbC.

The number of c-Fos labeled cells in the AcbSh did not increase after administration of haloperidol (0.2 mg/kg), which only showed a significant tendency ($p < .1$) of remedial effects on disrupted LI. In addition, we could not detect any changes after methamphetamine and/or blonanserin treatment in the c-Fos expression in the BLA, which is assumed to give substantial inputs to the NAc for the regulation of the LI. In contrast, the number of c-Fos positive neurons in the Ce was affected by both methamphetamine and blonanserin. Further study is needed to explain these patterns of c-Fos expression in the amygdala.

Blonanserin (0.3, 1.0, 3.0 mg/kg; not 0.1 mg/kg) increases neuronal firing in the locus coeruleus and ventral tegmental area and increases extracellular levels of norepinephrine and dopamine in the medial prefrontal cortex [13]. Blonanserin may activate the PFC function, but such activation was not detected as c-Fos immunoreactivity in the present study. Although the present interpretations are heavily based on the assumption that c-Fos immunolabeling can be used as a marker of neuronal activation [2], the lack of c-Fos expression does not preclude the possible existence of activated neurons, which has different transcriptional consequences.

5. Conclusion

The present results suggest that blonanserin ameliorates latent inhibition disrupted by methamphetamine predominantly via shell and core areas of the nucleus accumbens.

Acknowledgment

We thank Dainippon Sumitomo Pharma. Co., Ltd., Japan, for generously providing the blonanserin.

References

[1] E.D. Deeks, G.M. Keating, Blonanserin: a review of its use in the management of schizophrenia, CNS Drugs 24 (2010) 65–84.
[2] M. Dragunow, R. Faull, The use of c-fos as a metabolic marker in neuronal pathway tracing, J. Neurosci. Methods 29 (1989) 261–265.
[3] J. Feldon, I. Weiner, The latent inhibition model of schizophrenic attention disorder. Haloperidol and sulpiride enhance rats' ability to ignore irrelevant stimuli, Biol. Psychiatry 29 (1991) 635–646.
[4] E. Garcia, M. Robert, F. Peris, H. Nakamura, N. Sato, Y. Terazawa, The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia: a randomized, double-blind, placebo-controlled, multicentre study, CNS Drugs 23 (2009) 615–625.
[5] G. Gosselin, P. Oberling, G. Di Scala, Antagonism of amphetamine-induced disruption of latent inhibition by the atypical antipsychotic olanzapine in rats, Behav. Pharmacol. 7 (1996) 820–826.
[6] M. Horiguchi, H.Y. Meltzer, Blonanserin reverses the phencyclidine (PCP)-induced impairment in novel object recognition (NOR) in rats: role of indirect 5-HT partial agonism, Behav. Brain Res. 247 (2013) 158–164.
[7] T. Kinoshita, Long-term clinical study of blonanserin for schizophrenia (Japan-wide study), J. Clin. Psychopharmacol. 11 (2008) 135–153 (in Japanese).
[8] R.E. Lubow, Latent inhibition, Psychol. Bull. 79 (1973) 398–407.
[9] H. Matsuo, H. Abe, T. Ikeda, K. Ebihara, R. Takeda, T. Nishimori, Y. Ishida, Effect of aripiprazole on methamphetamine-induced disruption of latent inhibition in rats, J. Behav. Brain Sci. 1 (2011) 167–171.
[10] W.J. McBride, J.M. Murphy, S. Ikemoto, Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies, Behav. Brain Res. 101 (1999) 129–152.
[11] M. Murasaki, H. Nishikawa, T. Ishibashi, Dopamine-serotonin antagonist: receptor binding profile of a novel antipsychotics blonanserin, J. Clin. Psychopharmacol. 11 (2008) 845–854 (in Japanese).
[12] A.J. Nelson, K.E. Thur, R.R. Horsley, C. Spicer, C.A. Marsden, H.J. Cassaday, Reduced dopamine function within the medial shell of the nucleus accumbens enhances latent inhibition, Pharmacol. Biochem. Behav. 98 (2011) 1–7.
[13] K. Ohoyama, S. Yamamura, T. Hamaguchi, M. Nakagawa, E. Motomura, T. Shiroyama, H. Tanii, M. Okada, Effect of novel atypical antipsychotic, blonanserin, on extracellular neurotransmitter level in rat prefrontal cortex, Eur. J. Pharmacol. 653 (2011) 47–57.
[14] M. Oka, Y. Noda, Y. Ochi, K. Furukawa, T. Une, S. Kurumiya, K. Hino, T. Karasawa, Pharmacological profile of AD-5423, a novel antipsychotic with both potent dopamine-D2 and serotonin-S2 antagonist properties, J. Pharmacol. Exp. Ther. 264 (1993) 158–165.
[15] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, Academic Press, San Diego, 1998.
[16] H.H. Pothuizen, A.L. Jongen-Relo, J. Feldon, B.K. Yee, Double dissociation of the effects of selective nucleus accumbens core and shell lesions on impulsive-choice behaviour and salience learning in rats, Eur. J. Neurosci. 22 (2005) 2605–2616.
[17] P.R. Solomon, A. Crider, J.W. Winkelman, A. Turi, R.M. Kamer, L.J. Kaplan, Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: relationship to schizophrenic attention disorder, Biol. Psychiatry 16 (1981) 519–537.
[18] C.T. Tai, H.J. Cassaday, J. Feldon, J.N.P. Rawlins, Both electrolytic and excitotoxic lesions of nucleus accumbens disrupt latent inhibition of learning in rats, Neurobiol. Learn. Mem. 64 (1995) 36–48.
[19] N. Thiriet, J. Zwiller, S.F. Ali, Induction of the immediate early genes egr-1 and c-fos by methamphetamine in mouse brain, Brain Res. 919 (2001) 31–40.
[20] T. Une, S. Kurumiya, Pharmacological profile of blonanserin, J. Clin. Psychopharmacol. 10 (2007) 1263–1272 (in Japanese).
[21] E.C. Warburton, M.H. Joseph, J. Feldon, I. Weiner, J.A. Gray, Antagonism of amphetamine-induced disruption of latent inhibition in rats by haloperidol and ondansetron: implications for a possible antipsychotic action of ondansetron, Psychopharmacology 114 (1994) 657–664.
[22] I. Weiner, The "two-headed" latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment, Psychopharmacology 169 (2003) 257–297.
[23] I. Weiner, M. Arad, Using the pharmacology of latent inhibition to model domains of pathology in schizophrenia and their treatment, Behav. Brain Res. 204 (2009) 369–386.

[24] I. Weiner, G. Gal, J.N.P. Rawlins, J. Feldon, Differential involvement of the shell and core subterritories of the nucleus accumbens in latent inhibition and amphetamine-induced activity, Behav. Brain Res. 81 (1996) 123–133.
[25] I. Weiner, D. Schiller, I. Gaisler-Salomon, Disruption and potentiation of latent inhibition by risperidone: the latent inhibition model of atypical antipsychotic action, Neuropsychopharmacology 28 (2003) 499–509.
[26] I. Weiner, E. Shadach, R. Tarrasch, R. Kidron, J. Feldon, The latent inhibition model of schizophrenia: further validation using the atypical neuroleptic, clozapine, Biol. Psychiatry 40 (1996) 834–843.