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REGULAR RESEARCH ARTICLE

Comparison of Dopamine D_3 and D_2 Receptor Occupancies by a Single Dose of Blonanserin in Healthy Subjects: A Positron Emission Tomography Study With [^{11}C]-(+)-PHNO

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Abstract

Background: Blockade of D_3 receptor, a member of the dopamine D_2-like receptor family, has been suggested as a possible medication for schizophrenia. Blonanserin has high affinity in vitro for D_3 as well as D_2 receptors. We investigated whether a single dose of 12 mg blonanserin, which was within the daily clinical dose range (i.e., 8–24 mg) for the treatment of schizophrenia, occupies D_3 as well as D_2 receptors in healthy subjects.
Methods: Six healthy males (mean 35.7±7.6 years) received 2 positron emission tomography scans, the first prior to taking blonanserin, and the second 2 hours after the administration of a single dose of 12 mg blonanserin. Dopamine receptor occupancies by blonanserin were evaluated by [^{11}C]-(+)-PHNO.
Results: Occupancy of each region by 12 mg blonanserin was: caudate (range 64.3%–81.5%; mean±SD, 74.3±5.6%), putamen (range 60.4%–84.3%; mean±SD, 73.3%±8.2%), ventral striatum (range 40.1%–88.2%; mean±SD, 60.8%±17.1%), globus pallidus (range 65.8%–87.6%; mean±SD, 75.7%±8.6%), and substantia nigra (range 56.0%–88.7%; mean±SD, 72.4%±11.0%). Correlation analysis between plasma concentration of blonanserin and receptor occupancy in D_2-rich (caudate and putamen) and D_3-rich (globus pallidus and substantia nigra) regions showed that EC_{50} for D_2-rich region was 0.39 ng/mL (r=0.43) and EC_{50} for D_3-rich region was 0.40 ng/mL (r=0.79).
Conclusions: A single dose of 12 mg blonanserin occupied D_3 receptor to the same degree as D_2 receptor in vivo. Our results were consistent with previous studies that reported that some of the pharmacological effect of blonanserin is mediated via D_3 receptor antagonism.

Keywords: D_2 receptor, D_3 receptor, blonanserin, positron emission tomography

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Significance Statement

The focus of this study was on the occupancies of blonanserin for both dopamine D_2 and D_3 receptors in vivo. This study found that 12 mg blonanserin occupied D_3-rich region (i.e., 75.7% in globus pallidus and 72.4% in substantia nigra) as much as D_2-rich region (i.e., 74.3% in caudate and 73.3% in putamen) in healthy volunteers. Correlation analysis between the plasma concentration of blonanserin and receptor occupancy showed that the EC_{50} values of D_2-rich regions and D_3-rich regions are very similar (0.39 ng/mL, r=0.43 and 0.40 ng/mL, r=0.79). Our results indicated the possibility that some of the pharmacological effect of blonanserin is mediated via D_3 receptor antagonism.

Introduction

The mechanism of the antipsychotic effect of neuroleptics mainly focuses on the antagonism of D_2 receptor (Seeman, 2002). D_2 receptor antagonism can also induce some adverse effects (e.g., Parkinsonism, hyperprolactinemia), and therefore many researchers have been studying the effects of antipsychotics on the dopaminergic system and other monoaminergic systems, and also the association between pharmacological treatment and the change of monoaminergic systems in vivo.

Dopamine D_3 receptor, a member of the dopamine D_2-like receptor family, localizes in the limbic area and coexists with D_2 receptors in the substantia nigra as well as in many other areas in human brain. D_3 receptor has similarities to other members of the D_2-like receptor family, but D_3 receptor has very high affinity for dopamine and modulates dopamine release as an autoreceptor (Gross and Drescher, 2012). Some previous studies have reported that selective D_3 receptor antagonists might increase the extracellular dopamine concentrations in the medial prefrontal cortex (Gross and Drescher, 2012) and are also able to increase acetylcholine (Kuroki et al., 1999). These pharmacological studies and studies of rodent D_3 receptors have suggested that blockade of D_3 receptor might represent a new treatment mechanism for schizophrenia (Gross et al., 2013).

Many atypical antipsychotics and some typical antipsychotics have high affinities for both D_2 and D_3 receptors (Girgis et al., 2011). Recent technological progress has allowed us to visualize the distribution of D_3 receptors in vivo. [^{11}C]-(+)-PHNO is a D_3/D_2 agonist radioligand for positron emission tomography (PET) with preferential in vivo selectivity for dopamine D_3 over D_2 receptor (Willeit et al., 2006; Ginovart et al., 2007). Almost all of the signal of [^{11}C]-(+)-PHNO in both caudate and putamen represented D_2 receptor sites, while up to 100% of the signal in substantia nigra, 67% in globus pallidus, and 26% in ventral striatum represented D_3 receptor sites (Searle et al., 2010). An in vitro affinity study suggested that antipsychotics would occupy D_3 receptors as much as D_2 receptors, although antipsychotics reportedly occupied D_3 receptors moderately less than D_2 receptors (Girgis et al., 2011), and a PET study with [^{11}C]-(+)-PHNO reported that antipsychotics (i.e., clozapine, risperidone, olanzapine) did not decrease or even increased the in vivo nondisplaceable binding potential (BP_{ND}) of D_3 receptors in human brain (Graff-Guerrero et al., 2009). Another study also reported that chronically administered antipsychotics (i.e., clozapine, olanzapine, and haloperidol) showed lower selectivity for D_3 compared with D_2 receptors ex vivo than in vitro in rat brain (McCormick et al., 2010).

Blonanserin is an atypical antipsychotic, but unlike other atypical antipsychotics, the binding affinity for D_2 receptors (Ki=0.284 nM) is slightly higher than that for 5-HT_{2A} receptors (Ki=0.64 nM) in vitro (Murasaki et al., 2008). Blonanserin has high in vitro affinity for dopamine D_3 receptor (Ki=0.277 nM), similar to that for D_2 receptor (Ki=0.284 nM) (Baba et al., 2008). Blonanserin occupied a D_3-rich region (i.e., cerebellum lobe 9–10) similarly to a D_2-rich region (i.e., striatum) in rat brain, while risperidone, olanzapine, and aripiprazole did not (Baba et al., 2008). Blonanserin demonstrated efficacy against cognitive impairment induced by phencyclidine by inhibiting both dopamine D_3 and serotonin 5-HT_{2A} receptors in rat (Hida et al., 2015). Thus, blonanserin has been thought to have D_3 antagonism identical to D_2 and clinical efficacy by D_3 receptors. However, there has been no study of the evaluation of D_3 occupancy by blonanserin.

In this study, we investigated whether a clinical dose of blonanserin occupies D_3 receptors as well as D_2 receptors in healthy subjects.

Methods

Subjects

Six healthy male volunteers (range 27–46 years; mean±SD, 35.7±7.6) were enrolled. None had a history of present or past psychiatric, neurological, or somatic disorders, or alcohol or substance-related problems. After thorough explanation of the study, written informed consent was obtained from all participants. This study was approved by the review board of Nippon Medical School Hospital, Tokyo, Japan.

Study Design

This study was designed as a single administration, open-label protocol. Each subject underwent 2 PET scans, the first prior to taking blonanserin, and the second 2 hours after being administered of 12 mg blonanserin, which targeted the time-to-maximum blood concentration of blonanserin (Saruwatari et al., 2010).

PET Procedures

PET scans were carried out with Eminence SET-3000GCT-X (Shimadzu Corp) to measure regional brain radioactivity. This scanner provides 99 sections with an axial field of view of 26.0 cm. Spatial resolution was 3.45 mm in-plane and 3.72 mm axially full-width at half-maximum. A head fixation device was used during the scans. A 15-min transmission scan was done to correct for attenuation using a ^{137}Cs source. Dynamic PET scan was performed for 90 min (1 min×15, 5 min×15) after i.v. bolus injection of [^{11}C]-(+)-PHNO. Injected radioactivity was 196.4 to 385.0 MBq (348.8±64.2 (mean±SD MBq) for drug-free condition; 339.8±70.2 MBq for blonanserin condition). The injected mass of [^{11}C]-(+)-PHNO was 1.9 – 2.5 µg (2.2±0.3 µg for drug-free condition; 2.4±0.1 µg for blonanserin condition). Specific radioactivity was 41.7 – 95.4 GBq/µmol (77.7±7.5 GBq/µmol for drug-free condition; 77.9±7.5 GBq/µmol for blonanserin condition) at the time of injection.

MRI Procedures

Magnetic resonance (MR) images of the brain were acquired with 1.5T MR imaging, Intera 1.5T Achieve Nova (Philips Medical Systems) as proton density image (echo time = 17 msec; repetition time = 6000 msec; field of view = 22 cm, 2-dimensional, 256 × 256; slice thickness = 2 mm; number of excitations = 2). These images were used for analysis of the PET scans.

Measurement of Plasma Concentration of Blonanserin

Venous blood samples were taken just before second PET scans (2 hours after taking 12 mg blonanserin), collected in tubes containing EDTA-2Na, and centrifuged at 3000 rpm for 10 min at 4°C. Separated plasma samples were stored at -80°C until analysis. Plasma concentration was measured by validated method using high-performance liquid chromatography-tandem mass spectrometry with a target lower quantification limit of 0.001 ng/mL (Sekisui Medical Co., Ltd.).

Data Analysis

MR images were co-registered to summated PET images with the mutual information algorithm using PMOD (version 3.4; PMOD Technologies Ltd). Regions of interest (ROIs) were defined for the caudate, putamen, ventral striatum, globus pallidus, and substantia nigra, and were drawn manually in accordance with Tziortzi's study (Tziortzi et al., 2011). We defined the caudate and putamen as D_2-rich regions and the substantia nigra and globus pallidus as D_3-rich regions, according to Searle's study (Searle et al., 2010). ROIs were drawn manually on overlaid summated PET and co-registered MR images of each subject. By matching the targeted frame to the average of the first 10 frames (i.e., 0–10 minutes), motion corrections were conducted in 3 scans of 2 subjects because of head movements.

Quantitative estimate of binding of [^{11}C]-(+)-PHNO was performed using a simplified reference tissue model (Lammertsma and Hume, 1996), with the cerebellar cortex as reference region. This model has been validated to reliably estimate BP_{ND}, which compares the concentration of radioligand in the receptor-rich region with the receptor-free region (Innis et al., 2007), for [^{11}C]-(+)-PHNO (Ginovart et al., 2007).

Receptor occupancy by drugs was calculated by the following equation:

$$\text{Occupancy } (\%) = \left(BP_{NDbase} - BP_{NDdrug}\right) / BP_{NDbase} \times 100,$$

where occupancy is the receptor occupancy, BP_{NDbase} is BP_{ND} under drug-free condition, and BP_{NDdrug} is BP_{ND} under blonanserin condition.

We used a 1-site binding model, the same as a previous study (Graff-Guerrero et al., 2010). The relationship between plasma concentration and receptor occupancy was shown by the following equation:

$$\text{Occupancy } (\%) = E_{max} \times C / (EC_{50} + C) \times 100,$$

where C is the plasma concentration of drug, E_{max} is the maximum occupancy, and EC_{50} is the plasma concentration required to achieve 50% occupancy (Takano et al., 2006; Graff-Guerrero et al., 2010). E_{max} was fixed at 1 and $EC_{50} > 0$, the same as in previous occupancy studies (Takano et al., 2006; Graff-Guerrero et al., 2010). Since discrepancy of D_3 receptor occupancy between in vitro and in vivo studies has been reported (Graff-Guerrero et al., 2010; McCormick et al., 2010), correlations between plasma concentration and receptor occupancy were examined.

Results

Five subjects each completed two 90-min PET scans with [^{11}C]-(+)-PHNO. One subject provided partial data: the first PET scan (drug-free condition) was stopped at 70 min because of the subject's anxiety. We then included both conditions of 0 to 70 min PET data of this subject.

Figure 1 shows BP_{ND} of each ROI in each condition. Average BP_{ND} in drug-free condition was as follows: caudate (BP_{ND} range 1.04–1.68; mean ± SD, 1.53 ± 0.24), putamen (BP_{ND} range 1.28–2.06; 1.82 ± 0.29), ventral striatum (BP_{ND} range 1.59–2.85; 2.40 ± 0.43), globus pallidus (BP_{ND} range 1.56–2.68; 2.16 ± 0.40), and substantia nigra (BP_{ND} range 0.96–1.42; 1.06 ± 0.17). Average BP_{ND} in blonanserin condition was as follows: caudate (BP_{ND} range 0.27–0.60; 0.40 ± 0.12), putamen (BP_{ND} range 0.20–0.77; 0.50 ± 0.19), ventral striatum (BP_{ND} range 0.19–1.70; 0.99 ± 0.52), globus pallidus (BP_{ND} range 0.19–0.91; 0.54 ± 0.24), and substantia nigra (BP_{ND} range 0.11–0.47; 0.30 ± 0.13). The average level of receptor occupancy by a single dose of blonanserin 12 mg was as follows: caudate (range 64.3–81.5; 74.3 ± 5.6%), putamen (range 60.4–84.3; 73.3 ± 8.2%), ventral striatum (range 40.1–88.2; 60.8 ± 17.1%), globus pallidus (range 65.8–87.6; 75.7 ± 8.6%), and substantia nigra (range 56.0–88.7; 72.4 ± 11.0%) (Table 1).

The average drug concentration of blonanserin was 1.49 ± 0.88 (mean ± SD) ng/mL (range 0.58–2.90). Correlations between plasma concentration of blonanserin and receptor occupancy in D_2-rich and D_3-rich ROI are shown in Figure 2. EC_{50} was 0.39 ng/mL (df = 11, r = 0.43) for D_2-rich region and 0.40 ng/mL (df = 11, r = 0.79) for D_3-rich region.

Discussion

In this study, we examined the receptor occupancies in both D_2-rich and D_3-rich regions by a single dose of 12 mg blonanserin using [^{11}C]-(+)-PHNO PET. A single dose of 12 mg blonanserin occupied dopamine receptors in D_3-rich regions (i.e., substantia nigra, globus pallidus) as much as in D_2-rich regions (i.e., caudate, putamen). Receptor occupancy in the striatum by 12 mg blonanserin (74.3% for caudate and 73.3% for putamen) was almost the same as by [^{11}C]raclopride (68.5% for the striatum as calculated based on our previous data; Tateno et al., 2013). Thus, a single dose of 12 mg blonanserin, within the clinical daily dose range for the treatment of schizophrenia, occupied D_3 receptors to approximately the same extent as D_2 receptors. Thus, this is the first study to show that this dopamine antagonist occupied both D_2 and D_3 receptors at about the same levels.

Since dopaminergic hypofunction in the prefrontal cortex has been implicated in the pathogenesis of negative symptoms (Davis et al., 1991) and cognitive dysfunctions of schizophrenia (Sawaguchi, 2000), D_3 receptor antagonism might improve the negative symptoms and cognitive deficits of schizophrenia. Animal studies have reported that blonanserin showed cognitive efficacy via D_3 receptor antagonism and that it had a beneficial effect on prefrontal dopamine transmission (Gross et al., 2013; Nakajima et al., 2013; Hida et al., 2015). Other clinical studies showed that blonanserin induced improvements in verbal fluency and executive function (Tenjin et al., 2012; Hori et al., 2014), which might be related to the effect of this antipsychotic on dopamine transmission prefrontal cortex function. It has also been reported that functional

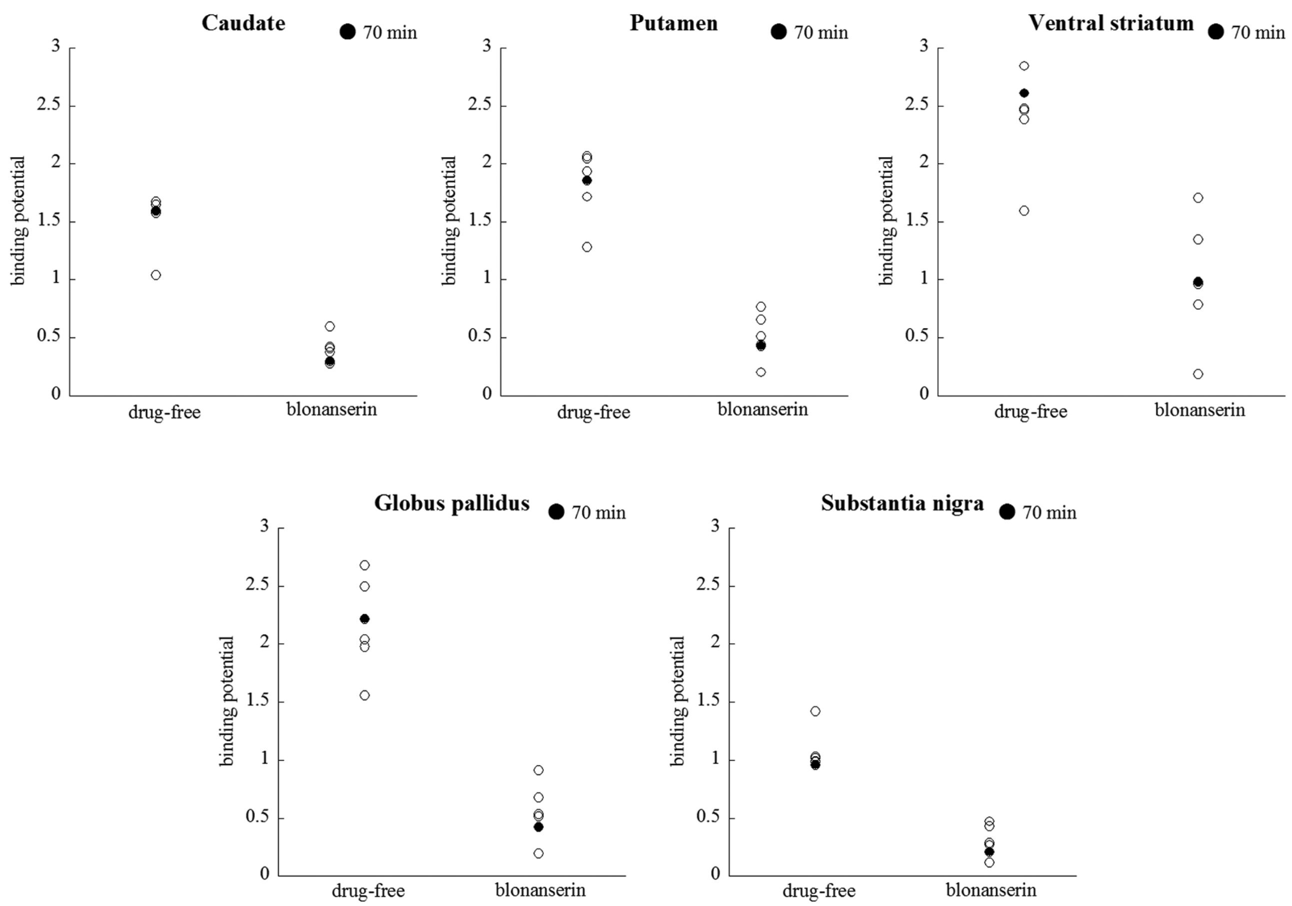

Figure 1. Binding potential (BP_{ND}) of [^{11}C]-(+)-PHNO for every region of interest before and after taking 12 mg blonanserin. Filled circles represent the subject with 70-min PET scans.

Table 1. Average Binding Potential and Occupancy of Dopamine Receptors in Each Region

Region of Interest	Drug-free	Blonanserin	Occupancy (%)
Caudate	1.53±0.24	0.40±0.12	74.3±5.6
Putamen	1.82±0.29	0.50±0.20	73.3±8.2
Globus pallidus	2.16±0.40	0.54±0.24	75.7±8.6
Ventral striatum	2.40±0.43	0.99±0.52	60.8±17.1
Substantia nigra	1.06±0.17	0.30±0.13	72.4±11.0

connectivity between the prefrontal cortex and salience/executive control networks negatively associated with midbrain D_3 receptor availability (Cole et al., 2011). Many PET studies have suggested that around 70% to 80% D_2 receptor occupancy in the striatum is required for an antipsychotic effect with a lower risk of extrapyramidal adverse effects (Farde et al., 1992; Nordström et al., 1993; Kapur et al., 2000). Previous studies showed that 150 mg of ABT-925, a selective D_3 receptor antagonist, possibly improves positive and negative symptoms of schizophrenia, and that it occupied about 30% of D_3 receptors in substantia nigra and globus pallidus (Graff-Guerrero et al., 2010; Bhathena et al., 2013). A recent study showed that a clinical dose of cariprazine, a D_3-preferring dual D_3/D_2 receptor partial agonist for the treatment of schizophrenia, occupied at least 76% of D_3 receptors, along with 45% of D_2 receptors (Girgis et al., 2016). However, the adequate degree of D_3 receptor occupancy for an antipsychotic effect or improvement of motivation and/or cognition has been unclear. Our result provided evidence that a single dose of 12 mg blonanserin antagonizes D_3 receptor as much as D_2 receptor, as has been indicated by previous studies (Baba et al., 2015), and therefore further study regarding what percentage of D_3 occupancy by antipsychotics might improve cognition could be beneficial for treatment strategies of schizophrenia.

The mechanism underlying the discrepancies between in vitro and in vivo bindings of several antipsychotics to dopamine D_3 receptors (Graff-Guerrero et al., 2010; McCormick et al., 2010) is still unclear. However, several explanations have been proposed. Girgis presented the upregulation scenario (Girgis et al., 2011). The study in baboons demonstrated binding of both D_2 and D_3 receptors by an acute dose of haloperidol (haloperidol: 70% of putamen and 61% of globus pallidus, clozapine: 43% of putamen and 21% of globus pallidus). Girgis further suggested that upregulation of D_3 receptor induced by chronic use of antipsychotics might affect the discrepancy between the results of in vitro affinity study and in vivo PET study (Girgis et al., 2011). Our study participants were healthy volunteers with a single administration, and our result was consistent with this scenario. Another explanation could be the influence of endogenous dopamine. Schotte reported that the D_2/D_3 potency ratios of antipsychotics (i.e., clozapine, olanzapine, risperidone, haloperidol) in vivo were 2 to 10 times higher than those of in vitro competitive binding experiments (Schotte et al., 1996), and they suggested that this effect was due to the in vivo inhibitory influence of endogenous dopamine. It has been suggested that antipsychotics inhibit D_2 and D_3 receptors in a dose-dependent manner, but the relationship between drug concentration and inhibitory effect differed

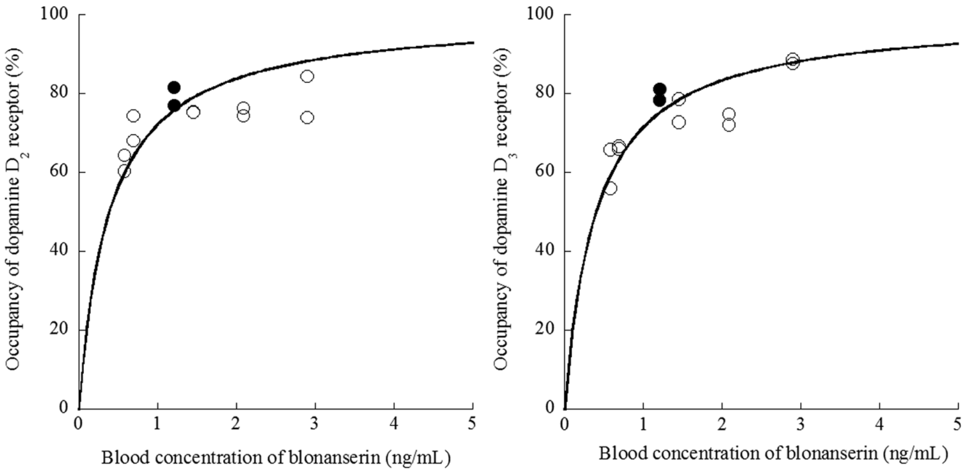

Figure 2. Correlation between receptor occupancy in D_2-rich (caudate and putamen) and D_3-rich (globus pallidus and substantia nigra) regions with [11C]-(+)-PHNO and plasma concentration of 12 mg blonanserin. Filled circles represent the subject with 70-min PET scans.

according to the respective antipsychotics. Tadori reported that most antipsychotics at clinical dose sufficiently antagonize D_2 receptor signals but not D_3 receptor signals, while blonanserin, haloperidol, and fluphenazine inhibit D_3 receptor at a similar level to D_2 receptor (Tadori et al., 2011). Their study suggested that a clinical dose of antipsychotics, except for blonanserin, haloperidol, and fluphenazine, preferentially inhibits D_2 receptor compared with D_3 receptor in vivo (Tadori et al., 2011).

There are several limitations to this study. First, we performed PET scan after only a single administration of an antipsychotic in 6 healthy subjects. It has been reported that chronic use of antipsychotics increases D_3 receptors among patients with schizophrenia (Graff-Guerrero et al., 2009). Another study of drug-naïve patients with schizophrenia showed that 2.5 weeks of antipsychotic treatment doubled BP_{ND} of D_3 receptors (Mizrahi et al., 2011). These studies indicated that the density of D_3 receptors in patients treated with antipsychotics might be different from that in healthy controls. Thus, to evaluate the precise relationship between drug concentration and both D_2 and D_3 receptor occupancies, further study with larger sample size, including patients, will be needed. Second, 1 of our 6 subjects provided only 70-min data from the PET scan. It was considered that this might affect the evaluation of BP_{ND}. However, the relationship between occupancy of receptors and drug concentration was almost unchanged when excluding this subject (in caudate: $r = 1.00$, $EC_{50} = 0.38$; in putamen: $r = 0.77$, $EC_{50} = 0.42$; in ventral striatum: $r = 0.62$, $EC_{50} = 0.82$; in globus pallidus: $r = 0.79$, $EC_{50} = 0.38$; in substantia nigra: $r = 0.85$, $EC_{50} = 0.46$).

In conclusion, our study using [11C]-(+)-PHNO demonstrated that a single dose of 12 mg blonanserin could occupy D_3 receptors to the same degree as D_2 receptors in vivo. Our results indicated the possibility that some of the pharmacological effect of blonanserin was mediated via D_3 receptor antagonism.

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Statement of Interest

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