別紙４

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

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ARTICLE

THEMATIC SECTION
New Developments in Schizophrenia Research

CINP

Effect of risperidone on high-affinity state of dopamine D_2 receptors: a PET study with agonist ligand [^{11}C](R)-2-CH_3O-N-n-propylnorapomorphine

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Abstract

The increased proportion of the high-affinity state of dopamine $D_{2/3}$ receptors ($D_{2,high}$) is assumed to correlate with dopamine hypersensitivity, implying a relationship with psychotic symptoms observed in psychiatric disorders such as schizophrenia. [^{11}C](R)-2-CH_3O-N-n-propylnorapomorphine ([^{11}C]MNPA), which has an agonistic property to dopamine D_2 receptors (D_2Rs), is expected to bind preferentially to $D_{2,high}$. The occupancy of dopamine D_2Rs by antagonists to receptors has not been investigated using [^{11}C]MNPA. We compared dopamine D_2R occupancies by risperidone, an antagonist to receptors, between [^{11}C]MNPA and [^{11}C]raclopride to confirm whether risperidone occupies $D_{2,high}$ and $D_{2,low}$ at almost identical proportions. PET studies were performed on 11 healthy men under resting condition and following oral administration of a single dose of risperidone (0.5–2.0 mg). Striatal receptor occupancy for each radioligand was calculated. The relationship between dose or plasma concentration of risperidone and dopamine D_2R occupancy was calculated. Striatal dopamine D_2R occupancies measured with [^{11}C]MNPA and [^{11}C]raclopride were 22–65% and 24–69%, respectively. In the striatum, ED_{50} values measured with [^{11}C]MNPA and [^{11}C]raclopride were 0.98 and 1.03 mg, respectively. The striatal ED_{50} values as calculated from plasma concentration were 9.15 ng/ml and 8.01 ng/ml, respectively. Almost identical occupancies and ED_{50} values were observed between the two radioligands, indicating that risperidone bound to $D_{2,high}$ and $D_{2,low}$ at almost identical proportions in a dose-dependent manner.

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Key words: Binding potential, dopamine D_2 receptor, receptor occupancy, risperidone, [^{11}C]MNPA.

Introduction

The dopaminergic neurotransmission system is of central interest in schizophrenia, and dopamine D_2 receptors (D_2Rs) are the main target in the treatment with antipsychotics (Seeman *et al.* 1975). Early *in-vitro* studies reported that dopamine D_2Rs have two interconvertible affinity states for endogenous dopamine, referred to as high-affinity ($D_{2,high}$) and low-affinity ($D_{2,low}$) states (De Lean *et al.* 1982; George *et al.* 1985; Richfield *et al.* 1989; Sibley *et al.* 1982). D_2R antagonists are reported to have equal affinity to both states of receptors, while endogenous dopamine preferentially binds to $D_{2,high}$ (Seneca *et al.* 2006). The increased proportion of $D_{2,high}$ is assumed to correlate with dopamine hypersensitivity, implying a relationship with psychotic symptoms observed in psychiatric disorders such as schizophrenia (Seeman *et al.* 2005).

[^{11}C]raclopride, an antagonist radioligand for dopamine D_2Rs, has been used to measure striatal

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dopamine D_2R binding with positron emission tomography (PET). [^{11}C]raclopride is thought to bind to both $D_{2,high}$ and $D_{2,low}$. Recently, several agonist radioligands for dopamine D_2Rs that are thought to bind preferentially to $D_{2,high}$ were developed, i.e. (−)-N-[^{11}C]propyl-norapomorphine ([^{11}C]NPA; Hwang *et al.* 2000), [^{11}]C(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol ([^{11}C]PHNO; Wilson *et al.* 2005), and [^{11}C](R)-2-CH3O-N-n-propylnorapomorphine ([^{11}C]MNPA). [^{11}C]MNPA has high selectivity and affinity to dopamine D_2Rs (IC_{50}: 1.02 nM, K_i: 0.17 nM; Gao *et al.* 1990; Neumeyer *et al.* 1990) and is believed to bind preferentially to the high-affinity state of dopamine $D_{2/3}Rs$.

The receptor occupancy for endogenous dopamine and dopamine agonists using [^{11}C]MNPA and [^{11}C]raclopride has been studied (Finnema *et al.* 2009; Seneca *et al.* 2006), but occupancy by dopamine antagonists was not fully investigated using [^{11}C]MNPA (Finnema *et al.* 2005). Most antipsychotic drugs are antagonists to dopamine D_2Rs, and the antipsychotic effects of such drugs have been considered to be mediated by blockade of dopamine D_2Rs. The degree of blockade can be evaluated by the occupancy of dopamine D_2Rs using PET. Because dopamine D_2R antagonists bind to both $D_{2,high}$ and $D_{2,low}$, occupancies of dopamine D_2Rs by antagonist antipsychotic drugs measured with [^{11}C]raclopride and [^{11}C]MNPA are expected to be the same.

In the present study, we measured dopamine D_2R occupancies by administration of a single dose of the antipsychotic risperidone as a dopamine D_2R antagonist using both [^{11}C]raclopride and [^{11}C]MNPA in healthy subjects. The dose–occupancy curves and the ED_{50} values in the putamen and caudate nuclei were compared between [^{11}C]raclopride and [^{11}C]MNPA.

Materials and methods

Subjects

Eleven healthy male volunteers (age range 21–39 yr, mean ± S.D. 27 ± 7.4yr) were recruited and written informed consent was obtained. They were healthy according to T1- and T2-weighted magnetic resonance (MR) imaging (Philips Medical Systems, The Netherlands) and blood (blood cell count, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma glutamyltransferase, creatine kinase, serum sodium, potassium, chlorine, blood urea nitrogen, serum creatinine, blood sugar) and urine screening tests. None had a history of psychiatric or neurological disorders, and they were free of physical disease. They had no history of current or previous drug abuse. The subjects were assigned to one of three groups according to risperidone dose: 0.5 mg ($n=5$), 1.0 mg ($n=3$), 2.0 mg ($n=3$). This study protocol was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Science, Chiba, Japan.

PET procedures

All PET data were obtained with a Siemens ECAT Exact HR+ system, which provides 63 sections with an axial field of view of 15.5 cm (Brix *et al.* 1997). The intrinsic spatial resolution was 4.3 mm in-plane and 4.2 mm full-width at half-maximum (FWHM) axially. With a Hanning filter (cut-off frequency 0.4 cycle/pixel), the reconstructed in-plane resolution was 7.5 mm FWHM. Imaging data were acquired in 3D mode. Scatter correction was performed (Watson *et al.* 1996). A thermoplastic head fixation device was used to minimize head movement during PET scanning. A 10-min transmission scan using a ^{68}Ge–^{68}Ge line source was performed for attenuation correction.

PET studies were performed under resting condition (baseline study) and oral administration of risperidone (drug challenge study) on separate days. The average interval between the two studies was 8.3 ± 2.8 d. After intravenous rapid bolus injection of [^{11}C]raclopride, dynamic PET scanning was performed for 60 min. One hour after the end of [^{11}C]raclopride PET measurement, dynamic PET scanning was performed for 90 min after intravenous rapid bolus injection of [^{11}C]MNPA. The frame sequence comprised nine 20-s frames, five 60-s frames, four 120-s frames, eleven 240-s frames and six 300-s frames for [^{11}C]-MNPA, and twelve 20-s frames, sixteen 60-s frames and ten 240-s frames for [^{11}C]raclopride. Injected radioactivities for [^{11}C]MNPA and [^{11}C]raclopride under baseline conditions were 208–248 MBq and 207–241 MBq, respectively, and under drug challenge 214–235 MBq and 182–232 MBq, respectively, for [^{11}C]MNPA and [^{11}C]raclopride. The specific radioactivities for [^{11}C]MNPA and [^{11}C]raclopride under baseline conditions were 148–429 GBq/μmol and 222–736 GBq/μmol, respectively, and under drug challenge 103–411 GBq/μmol and 211–545 GBq/μmol, respectively.

Measurement of plasma concentration of risperidone

In the drug challenge study, 0.5–2 mg risperidone was orally administered 2 h prior to the start of PET scanning with [^{11}C]raclopride. To determine the plasma concentration of risperidone and its active metabolite

(9-hydroxy-risperidone), venous blood samples were drawn at 10–15 min before, and at 1 h, 2 h, 3 h, 4 h, 5.5 and 7 h after its oral administration.

The series of blood samples of each subject were collected in heparinized tubes and centrifuged for 10 min at 3000 rpm. All plasma samples were stored at −20 °C. The plasma concentrations of risperidone and 9-hydroxy-risperidone were determined using the liquid chromatography coupled to mass spectrometry/mass spectrometry (LC–MS/MS) method with a target lower limit of quantification of 0.10 ng/ml (Johnson & Johnson Pharmaceutical Research and Development L. L. C., Belgium). Since risperidone and 9-hydroxy risperidone have similar binding profiles to neuroreceptors (Leysen *et al.* 1994), the sum of the plasma concentrations of risperidone and 9-hydroxy-risperidone was used as the plasma concentration of the antipsychotic drug (Ito *et al.* 2009*a*; Leysen *et al.* 1994).

MR imaging

MR images were acquired with a 1.5-T MR scanner (Philips Medical Systems, The Netherlands). 3D volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (TE 9.2 ms, TR 21 ms, flip angle 30°, field of view 256 mm, acquisition matrix 256 × 256, slice thickness 1 mm).

Data analysis

All data analyses were performed with PMOD 3.0 software (PMOD Technologies, Switzerland). Volumes of interest (VOIs) were defined for the caudate head, putamen, dorsal striatum (caudate head and putamen) and cerebellar cortex. For accurate definition of each VOI, each MR image was co-registered to the corresponding summated PET image. VOIs were drawn manually on each summated PET image with reference to each co-registered MR image. Subsequently, the data of each VOI were applied to each dynamic PET image. In the present study, we applied VOIs obtained from individual PET space according to the previous quantitative study of [^{11}C]MNPA in humans (Otsuka *et al.* 2009). To obtain regional time–activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted *vs.* time.

Dopamine D_2R binding was quantified using a three-parameter simplified reference tissue model (Lammertsma & Hume, 1996). The cerebellar cortex was used as reference tissue due to its negligible density of dopamine D_2Rs (Suhara *et al.* 1999). This model allows the estimation of binding potential (BP_{ND}). BP_{ND} was defined as a follows:

$$BP_{ND} = f_{ND} \times B_{max}/K_d, \quad (1)$$

where f_{ND} is the free fraction of radioligand in the non-displaceable tissue compartment, B_{max} the neuroreceptor density, and K_d the dissociation constant of radioligand to receptors (Innis *et al.* 2007). The dopamine D_2R occupancies by risperidone were calculated as follows:

$$\text{occupancy } (\%) = (BP_{base} - BP_{drug})/BP_{base} \times 100, \quad (2)$$

where BP_{base} is the BP_{ND} in the drug-free state, and BP_{drug} the BP_{ND} under administration of risperidone (Takano *et al.* 2004, 2006; Yasuno *et al.* 2001). The relationship between the dose or the plasma concentration of antipsychotic drug and dopamine D_2R occupancy can be expressed as follows:

$$\text{occupancy } (\%) = D/(D + ED_{50}) \times 100, \quad (3)$$

where D is the dose or the sum of the plasma concentrations of risperidone and 9-hydroxy-risperidone (Nyberg *et al.* 1999), and ED_{50} is the plasma concentration required to induce 50% occupancy. The maximal occupancy of D_2Rs was restricted to 100% to reflect the expected maximal occupancy. All the regression analyses were performed using Kaleida Graph 4.01 software (Synergy Software, USA). The regression line was fitted according to equation (3), with calculation of the ED_{50} values and regression coefficients for each radioligand. The mean plasma concentration values at the start and end of PET scanning were used for the calculation of ED_{50} values.

Results

Baseline BP_{ND} values of [^{11}C]MNPA were 0.84 ± 0.1 in the striatum, 0.67 ± 0.1 in the caudate nuclei and 0.93 ± 0.1 in the putamen. Baseline BP_{ND} values of [^{11}C]raclopride were 3.17 ± 0.4 in the striatum, 2.83 ± 0.4 in the caudate nuclei and 3.37 ± 0.4 in the putamen (Table 1).

The dopamine D_2R occupancies using [^{11}C]MNPA ranged from 22% to 66% for the striatum, 34–78% for the caudate nuclei, and 17–67% for the putamen in the three dose groups. Receptor occupancies using [^{11}C]raclopride ranged from 18% to 70% for the striatum, 22–72% for the caudate nuclei, and 17–69% for the putamen.

Significant positive correlations of dopamine D_2R occupancies between [^{11}C]raclopride and [^{11}C]MNPA were observed in the caudate nuclei and putamen (caudate nuclei: $r = 0.65$, $p = 0.04$; putamen: $r = 0.86$, $p = 0.01$).

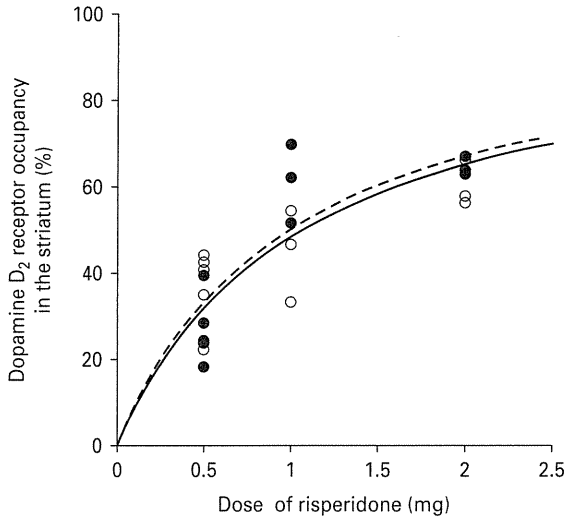

Fig. 1. The relationship between dopamine D_2 receptor occupancy in the striatum and risperidone dose. Open symbols (○) and solid curve (——) indicate receptor occupancy with [^{11}C]MNPA and its fitting curve, and solid symbols (●) and dashed curve (– – –) indicate receptor occupancy with [^{11}C]raclopride and its fitting curve, respectively. ED_{50} in the striatum was 1.08 and 1.00 mg for [^{11}C]MNPA and [^{11}C]raclopride, respectively.

The relationship between dopamine D_2R occupancy in the striatum and risperidone dose are shown in Fig. 1. These relationships are well described by equation (3) (striatum: $r=0.86$ and $r=0.68$; caudate nuclei: $r=0.86$ and $r=0.62$; putamen: $r=0.85$ and $r=0.78$ for [^{11}C]raclopride and [^{11}C]MNPA, respectively). The ED_{50} values calculated from [^{11}C]raclopride and [^{11}C]MNPA, respectively, were 1.00 mg ($r=0.86$) and 1.08 mg ($r=0.68$) in the striatum, 0.88 mg ($r=0.86$) and 0.80 mg ($r=0.62$) in the caudate nuclei, and 1.07 ($r=0.85$) mg and 1.00 mg ($r=0.78$) in the putamen.

The sum of plasma concentrations of risperidone and 9-hydroxy-risperidone during [^{11}C]raclopride and [^{11}C]MNPA studies, averaged between the start and end of each scanning, was 9.37 ± 4.89 ng/ml and 7.74 ± 3.91 ng/ml (mean$\pm$S.D.), respectively. The relationship between dopamine D_2R occupancy in the striatum and the sum of plasma concentrations of risperidone and 9-hydroxy-risperidone are shown in Fig. 2. The ED_{50} values from the plasma concentration–occupancy curves with [^{11}C]raclopride and [^{11}C]MNPA, respectively, were 9.15 ng/ml ($r=0.91$) and 8.32 ng/ml ($r=0.36$) in the striatum, 8.00 ng/ml ($r=0.88$) and 6.12 ng/ml ($r=0.53$) in the caudate nuclei, and 9.75 ng/ml ($r=0.92$) and 7.70 ng/ml ($r=0.74$) in the putamen.

Table 1. The range of dopamine D_2 receptor binding potential values of [^{11}C]MNPA and [^{11}C]raclopride by dose of risperidone

	Baseline	0.5 mg	1.0 mg	2.0 mg
[^{11}C]MNPA				
Caudate head	0.40–0.81	0.32–0.49	0.21–0.33	0.16–0.39
Putamen	0.70–1.22	0.48–0.79	0.45–0.52	0.28–0.44
Dorsal striatum	0.84–0.13	0.44–0.65	0.40–0.40	0.26–0.41
[^{11}C]raclopride				
Caudate head	2.19–3.36	1.65–2.28	0.66–1.22	0.84–1.1
Putamen	2.56–4.11	2.37–2.86	1.00–1.44	1.03–1.44
Dorsal striatum	2.55–3.84	2.15–2.65	0.87–1.37	0.99–1.28

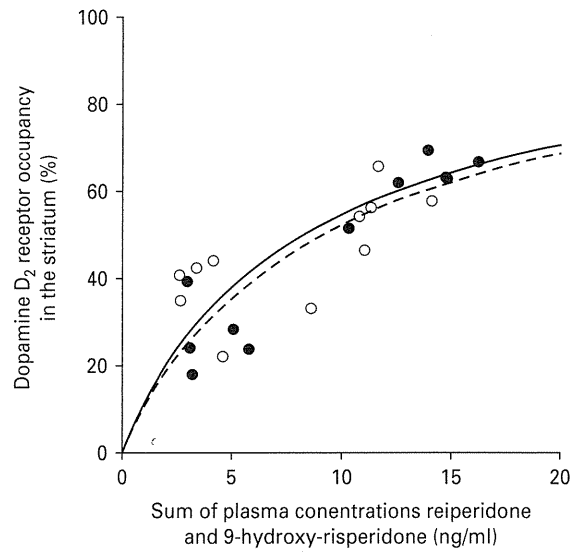

Fig. 2. The relationship between dopamine D_2 receptor occupancy in the striatum and the sum of plasma concentrations of risperidone and 9-hydroxy-risperidone. Open symbols (●) and solid curve (——) indicate receptor occupancy with [^{11}C]MNPA and its fitting curve, and solid symbols (○) and dashed curve (– – –) indicate receptor occupancy with [^{11}C]raclopride and its fitting curve, respectively. ED_{50} in the striatum was 8.32 ng/ml and 9.15 ng/ml for [^{11}C]MNPA and [^{11}C]raclopride, respectively.

Discussion

The present study demonstrated dopamine D_2R occupancies by risperidone measured with both [^{11}C]MNPA and [^{11}C]raclopride, i.e. the effects of risperidone on $D_{2,high}$ and $D_{2,low}$. The dopamine D_2R occupancies and ED_{50} values measured by [^{11}C]raclopride under risperidone administration were in agreement with most previous studies (Kapur *et al.* 1999; Nyberg *et al.* 1999;

Yasuno *et al.* 2001). In addition, the dose–occupancy curves and ED_{50} values with [^{11}C]MNPA were almost identical to those of [^{11}C]raclopride. Therefore, these results indicate that risperidone binds to both $D_{2,high}$ and $D_{2,low}$ at almost identical proportions. This is in accord with the report that risperidone is an antagonist for dopamine D_2Rs (Leysen *et al.* 1994) and has equal binding affinity to both $D_{2,high}$ and $D_{2,low}$ receptors (Seneca *et al.* 2006).

The [^{11}C]MNPA PET studies began 2 h after the start of the [^{11}C]raclopride PET studies. The sums of the plasma concentrations of risperidone and 9-hydroxyrisperidone were thus slightly higher during [^{11}C]-raclopride studies (9.37 ± 4.89 ng/ml) than during [^{11}C]MNPA studies (7.74 ± 3.91 ng/ml), raising the possibility that the occupancy of [^{11}C]MNPA by dose could be underestimated in the present study. However, the ED_{50} value calculated by plasma concentrations showed almost identical values with the ED_{50} value by dose.

With regard to the *in-vivo* proportion of $D_{2,high}$ to $D_{2,low}$ in dopamine D_2Rs, several arguments have been put forward. Seneca *et al.* (2006) demonstrated that the sensitivity of striatal uptake of [^{11}C]MNPA is greater than that of [^{11}C]raclopride in response to amphetamine-induced dopamine release. It was indicated that [^{11}C]MNPA BP_{ND} was ~50% more sensitive to change than [^{11}C]raclopride to amphetamine-induced increase in synaptic dopamine. These authors suggested that 61% of the D_2Rs are configured in the high-affinity state (10% occupied by dopamine at baseline, 23% synaptic and 28% extrasynaptic) (Seneca *et al.* 2006). Narendran *et al.* (2010) also observed greater [^{11}C]NPA BP_{ND} reduction in response to amphetamine-induced dopamine release compared to [^{11}C]raclopride in healthy humans (Narendran *et al.* 2010). Moreover, Seeman (2009) demonstrated in their *ex-vivo* study that the dopamine agonist NPA inhibited [^{3}H]PHNO binding more than [^{3}H]raclopride did in amphetamine-sensitized rodents, indicating *in-vivo* competition of NPA to $D_{2,high}$ (Seeman, 2009). These experimental observations might provide psychopharmacological basis of dopamine D_2R hypersensitivity in patients with schizophrenia, i.e. use of psychostimulants worsens psychotic symptoms in patients with schizophrenia (Curran *et al.* 2004; Lieberman *et al.* 1987).

In contrast, Finnema *et al.* (2009) did not find distinguishable ID_{50} and K_i values of apomorphine for dopamine D_2Rs when measured with [^{11}C]MNPA and [^{11}C]raclopride (Finnema *et al.* 2009). *In-vitro* binding studies demonstrated that apomorphine binds to $D_{2,high}$ with 30- to 60-fold higher affinity compared to $D_{2,low}$ (De Lean *et al.* 1982; Sibley *et al.* 1982), and they suggest that almost all dopamine D_2Rs are in a high-affinity state at *in-vivo* condition. These findings might be the case for dopamine D_2 antagonists, partial as well as full agonists. Peng *et al.* (2010) found no significant differences of dopamine D_2R occupancy with [^{3}H]raclopride, [^{3}H]MNPA and [^{3}H]PHNO by using quinpirole (full agonist), aripiprazole (partial agonist), and haloperidol (antagonist) (Peng *et al.* 2010). A similar finding was observed in a previous *ex-vivo* study with [^{11}C]PHNO (McCormick *et al.* 2008). In clinical investigations, there is no clear evidence for the $D_{2,high}$ to $D_{2,low}$ proportion in dopamine D_2Rs. While ~20% differences of dopamine D_2R occupancy between [^{11}C]MNPA and [^{11}C]raclopride were observed in long-term treated patients with schizophrenia by Graff-Guerrero *et al.* (2009*a*), they found no significant differences of [^{11}C]PHNO binding in patients with schizophrenia-spectrum disorder amidst an acute psychotic episode group compared to control group (Graff-Guerrero *et al.* 2009*b*). In any case, further *in-vivo* investigations would be needed to elucidate the plausible ratio of $D_{2,high}$ to $D_{2,low}$. In particular, an *in-vivo* human receptor occupancy PET study using dopamine full agonists and/or partial agonists (e.g. an antipsychotic agent aripiprazole; Mamo *et al.* 2007) might help elucidate the $D_{2,high}$ and $D_{2,low}$ proportions in dopamine D_2Rs.

It is reported that a part of dopamine D_2R agonist radioligands shows higher affinity for dopamine D_3Rs. [^{11}C]PHNO is assumed to have ~50-fold higher selectivity to dopamine D_3Rs than to dopamine D_2Rs (Freedman *et al.* 1994; Narendran *et al.* 2006). This indicates that the observed differences of K_i value between [^{11}C]PHNO and [^{11}C]raclopride could be interpreted as the difference between D_2 and D_3 binding property. Meanwhile, a previous *ex-vivo* study showed that [^{11}C]MNPA has almost identical affinity to dopamine D_2 and D_3 receptors [2.21 nM (D_2) and 2.02 nM (D_3)] (Skinbjerg *et al.* 2009).

The dopamine D_2 antagonist administered could bind to dopamine D_2 autoreceptors as well as to post-synaptic dopamine D_2Rs. Blockade of dopamine D_2 autoreceptors could regulate dopaminergic neurotransmission in the present study. A recent human PET study on acute administration of the dopamine D_2 antagonist (risperidone) showed a stabilizing effect of risperidone on dopamine synthesis (Ito *et al.* 2009*b*). That study raised the possibility that acute administration of dopamine D_2R antagonist affects post-synaptic receptors by regulating the dopaminergic neurotransmission. Further study will be needed to elucidate the effect on dopamine D_2 autoreceptors.

In conclusion, dopamine D_2R occupancies by administration of risperidone, a dopamine D_2R antagonist, were measured in healthy subjects using both [^{11}C]raclopride and [^{11}C]MNPA. Almost identical occupancies were observed with the two radioligands, implying that risperidone binds to $D_{2,high}$ and $D_{2,low}$ at almost identical proportions in a dose-dependent manner. The present results of dose–occupancy curves with both radioligands also suggest that the same therapeutic window could be applicable to $D_{2,high}$ and for dopamine D_2Rs including both $D_{2,high}$ and $D_{2,low}$.

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Statement of Interest

None.

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Behavioral/Systems/Cognitive

Relation between Presynaptic and Postsynaptic Dopaminergic Functions Measured by Positron Emission Tomography: Implication of Dopaminergic Tone

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Both presynaptic and postsynaptic dopaminergic functions can be estimated by positron emission tomography (PET). While both presynaptic and postsynaptic dopaminergic functions would be regulated by corresponding genes and related to personality traits, the relation between presynaptic and postsynaptic functions in terms of interindividual variation has hardly been investigated. In the present study, both striatal dopamine D_2 receptor binding and endogenous dopamine synthesis rate were measured in the same healthy subjects using PET with [^{11}C]raclopride and L-[β-^{11}C]DOPA, respectively, and these two parameters were compared. Two PET studies with [^{11}C]raclopride and L-[β-^{11}C]DOPA were performed sequentially at rest condition on 14 healthy men. For [^{11}C]raclopride PET, the binding potential was calculated by the reference tissue model method. For L-[β-^{11}C]DOPA PET, the endogenous dopamine synthesis rate was estimated by graphical analysis. A significant negative correlation was observed between the binding potential of dopamine D_2 receptors and endogenous dopamine synthesis rate ($r = -0.66, p < 0.05$). Although the interindividual variation of binding potential of [^{11}C]raclopride would be due to both the interindividual difference in the receptor density and that in the concentration of endogenous dopamine in the synaptic cleft, the negative correlation between parameters for both presynaptic and postsynaptic functions might indicate a compensative relation between the two functions.

Introduction

The central dopaminergic system is of interest in the pathophysiology of schizophrenia and other neuropsychiatric disorders. Both presynaptic and postsynaptic dopaminergic functions can be estimated by positron emission tomography (PET) using several radiotracers. The binding of dopamine receptors representing postsynaptic functions in the striatum can be measured for each of D_1 and D_2 subtypes using [^{11}C]SCH23390 (Halldin et al., 1986; Farde et al., 1987) and [^{11}C]raclopride (Farde et al., 1985; Köhler et al., 1985; Ito et al., 1998), respectively. The relative activity of cerebral aromatic L-amino acid decarboxylase (AADC) representing endogenous dopamine synthesis rate measured by 6-[^{18}F]fluoro-L-DOPA (Gjedde, 1988; Gjedde et al., 1991; Huang et al., 1991) and L-[β-^{11}C]DOPA (Hartvig et al., 1991; Tedroff et al., 1992) can indicate the presynaptic dopaminergic function. Using PET, interindividual variations in both presynaptic and postsynaptic dopaminergic functions in the striatum of normal living human brain were observed (Ito et al., 2008).

It has been reported that the dopamine D_2 receptor density was related to polymorphisms in the dopamine D_2 receptor gene in humans (Jönsson et al., 1999). Genotypes of human monoamine-synthesizing enzymes, e.g., tyrosine hydroxylase (TH) and AADC, were also determined (Nagatsu, 1991), and TH genotypes were reported to participate in the regulation of monoamine turnover in the CNS (Jönsson et al., 1996). It has been reported that dopamine D_2 receptor binding and the endogenous dopamine synthesis rate measured by PET were correlated with personality traits (Farde et al., 1997; Breier et al., 1998; Laakso et al., 2003).

While both presynaptic and postsynaptic dopaminergic functions would be regulated by corresponding genes and related to personality traits, the relation between presynaptic and postsynaptic functions in interindividual variation has hardly been investigated. In the present study, both striatal dopamine D_2 receptor binding and endogenous dopamine synthesis rate were measured in the same healthy subjects using PET with [^{11}C]raclopride and L-[β-^{11}C]DOPA, respectively, and these two parameters were compared.

Materials and Methods

Subjects. The study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan. Fourteen healthy men [20–29 years of age, 23.8 ± 2.9 years

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(mean ± SD)] were recruited and written informed consent was obtained. The subjects were free of somatic, neurological, or psychiatric disorders on the basis of their medical history and magnetic resonance (MR) imaging of the brain. They had no history of current or previous drug abuse.

PET procedures. All PET studies were performed with a Siemens ECAT Exact HR+ system, which provides 63 sections with an axial field of view of 15.5 cm (Brix et al., 1997). The intrinsic spatial resolution was 4.3 mm in-plane and 4.2 mm full-width at half-maximum (FWHM) axially. With a Hanning filter (cutoff frequency: 0.4 cycle/pixel), the reconstructed in-plane resolution was 7.5 mm FWHM. Data were acquired in three-dimensional mode. Scatter was corrected (Watson et al., 1996). A 10 min transmission scan using a ^{68}Ge–^{68}Ga line source was performed for correction of attenuation. A head fixation device with thermoplastic attachments for individual fit minimized head movement during PET measurements. Two PET studies with [^{11}C]raclopride and L-[β-^{11}C]DOPA were performed sequentially at rest condition. After intravenous rapid bolus injection of [^{11}C]raclopride, dynamic PET scanning was performed for 60 min. After 1 h from the end of [^{11}C]raclopride PET measurement, dynamic PET scanning was performed for 89 min after intravenous rapid bolus injection of L-[β-^{11}C]DOPA. In one subject, the L-[β-^{11}C]DOPA PET measurement was performed 5 d after the [^{11}C]raclopride PET measurement. The frame sequence consisted of twelve 20 s frames, sixteen 1 min frames, and ten 4 min frames for [^{11}C]raclopride, and seven 1 min frames, five 2 min frames, four 3 min frames, and twelve 5 min frames for L-[β-^{11}C]DOPA. The radioactivity injected was 194–230 MBq and 342–395 MBq for [^{11}C]raclopride and L-[β-^{11}C]DOPA, respectively. The specific radioactivity was 168–517 GBq/μmol and 26–88 GBq/μmol for [^{11}C]raclopride and L-[β-^{11}C]DOPA, respectively. A venous blood sample was taken at the beginning of L-[β-^{11}C]DOPA PET scanning for measurement of natural neutral amino acid (NAA) concentration in plasma. NAA concentration was measured by HPLC (L-8500 amino acid analyzer system, Hitachi). The amino acids are phenylalanine, tryptophan, leucine, methionine, isoleucine, tyrosine, histidine, valine, and threonine, which are transported via the same carrier at the blood–brain barrier as L-DOPA (Sugaya et al., 2001). A weighted sum of the NAAs, which was the L-DOPA-corresponding concentration of the nine NAAs for the carrier system, was calculated according to our previous study (Ito et al., 2006).

All MR imaging studies were performed with a 1.5 tesla MR scanner (Philips Medical Systems). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (TE: 9.2 ms; TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256 × 256; slice thickness: 1 mm).

Regions of interest. All MR images were coregistered to the PET images with the statistical parametric mapping (SPM2) system (Friston et al., 1990). Regions of interest (ROIs) were drawn on coregistered MR images and transferred to the PET images. ROIs were defined for the cerebellar cortex, caudate head, putamen, and occipital cortex. Each ROI was drawn in three adjacent sections and data were pooled to obtain the average radioactivity concentration for the whole volume of interest. The radioactivity concentration of the striatum was calculated as the average of values of caudate head and putamen. To obtain regional time–activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time. No software correction for head movement during PET measurements was applied to the dynamic PET images.

Calculation of dopamine D_2 receptor binding. For PET studies with [^{11}C]raclopride, the binding potential (BP_{ND}) was calculated by the reference tissue model method (Lammertsma and Hume, 1996; Lammertsma et al., 1996). With this method, the time–activity curve in the brain region is described by that in the reference region with no specific binding, assuming that both regions have the same level of nondisplaceable radioligand binding:

$$C_i(t) = R_1 \cdot C_r(t) + \{k_2 - R_1 \cdot k_2/(1 + BP_{ND})\} \cdot C_r(t) \otimes \exp\{-k_2 \cdot t/(1 + BP_{ND})\},$$

where C_i is the radioactivity concentration in a brain region; C_r is the radioactivity concentration in the reference region; R_1 is the ratio of K_1/K_1' (K_1, influx rate constant for the brain region; K_1', influx rate constant for the reference region); k_2 is the efflux rate constant for the brain region; and 196 denotes the convolution integral. BP_{ND} is defined as $BP_{ND} = f_{ND}B_{avail}/K_D$, where B_{avail} is the receptor density available to bind radiotracer *in vivo* and K_D is the dissociation constant indicating affinity of radiotracer to receptors (Innis et al., 2007). f_{ND} is the free fraction of radiotracer in the compartment of nondisplaceable binding. In this analysis, three parameters (BP_{ND}, R_1, and k_2) were estimated by nonlinear least-squares curve fitting. The cerebellum was used as reference region.

Calculation of dopamine synthesis rate. The uptake rate constant for L-[β-^{11}C]DOPA indicating the dopamine synthesis rate was estimated using graphical analysis (Patlak and Blasberg, 1985; Gjedde, 1988; Ito et al., 2006), which allows for the calculation of the uptake rate constant (k_{ref}) using time–activity data in a reference brain region with no irreversible binding. k_{ref} values can be estimated by using simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_{ref} \cdot \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(\tau)} + F \quad t > t^*,$$

where C_i and C_i' are the total radioactivity concentrations in a brain region with and without irreversible binding, respectively, and t^* is the equilibrium time of the compartment for unchanged radiotracer in brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after time t^*, yields a straight line with the slope k_{ref} and intercept F. In the present study, the occipital cortex was used as a reference region with no irreversible binding, because this region is known to have the lowest dopamine concentration (Brown et al., 1979) and lowest AADC activity (Lloyd and Hornykiewicz, 1972). The equilibrium time t^* was set to be 29 min, and data plots of 29–89 min were used for linear least-squares fitting (Ito et al., 2006, 2007).

Table 1. The binding potential (BP_{ND}) of [^{11}C]raclopride studies and dopamine synthesis rate k_{ref} of L-[β-^{11}C]DOPA studies

	Caudate head	Putamen	Striatum
BP_{ND}	2.66 ± 0.23	3.40 ± 0.29	3.15 ± 0.26
k_{ref}(min^{-1})	0.0118 ± 0.0019	0.0135 ± 0.0016	0.0129 ± 0.0015

Values are mean ± SD.

Results

The BP_{ND} of the [^{11}C]raclopride studies and dopamine synthesis rate k_{ref} of the L-[β-^{11}C]DOPA studies are shown in Table 1. Weighted sum of the NAAs in plasma was 1262 ± 186 nmol/ml (mean ± SD) for L-[β-^{11}C]DOPA studies. No significant correlation was observed between weighted sum of the NAAs and the dopamine synthesis rate k_{ref} of L-[β-^{11}C]DOPA.

Relations between BP_{ND} and k_{ref} in the striatum are shown in Figure 1. A significant negative correlation was observed between BP_{ND} and k_{ref} ($y = -0.0038x + 0.025$, x: BP_{ND}, y: k_{ref}, $r = -0.66$, $p < 0.05$). A trend of negative correlation was observed between BP_{ND} and k_{ref} in the putamen ($y = -0.0028x + 0.023$, x: BP_{ND}, y: k_{ref}, $r = -0.51$, $p < 0.1$). No significant correlation was observed in the caudate head ($y = -0.0028x + 0.019$, x: BP_{ND}, y: k_{ref}, $r = -0.35$). Typical images of BP_{ND} of subjects with low and high BP_{ND} and corresponding images indicating dopamine synthesis rate are shown in Figure 2.

Discussion

To our knowledge, there are only a few reports concerning the relation between striatal dopamine D_2 receptor binding and endogenous dopamine synthesis ability in the living human brain, and no significant correlation was observed (Heinz et al., 2005; Kienast et al., 2008). Although the coefficient of variation of