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Attitude of young psychiatrists toward coercive measures in psychiatry: a case vignette study in Japan

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Abstract

Background: Every psychiatrist must pay careful attention to avoid violating human rights when initiating coercive treatments such as seclusion and restraint. However, these interventions are indispensable in clinical psychiatry, and they are often used as strategies to treat agitated patients. In this study, we investigated young psychiatrists' attitudes toward psychiatric coercive measures.

Methods: A total of 183 young psychiatrists participated as subjects in our study. A questionnaire with a case vignette describing a patient with acute psychosis was sent to the study subjects via the Internet or by mail. This questionnaire included scoring the necessity for hospitalization, and the likelihood of prescribing seclusion and/or restraint, on a 9-point Likert scale (with 9 indicating strong agreement).

Results: There was general agreement among the study subjects that the case should be admitted to a hospital (8.91 ± 0.3) and secluded (8.43 ± 1.0). The estimated length of hospitalization was 13.53 ± 6.4 weeks. Regarding the likelihood of prescribing restraint, results showed great diversity (5.14 ± 2.5 on 9-point scale); psychiatrists working at general hospitals scored significantly higher (6.25 ± 2.5) than those working at university hospitals (5.02 ± 2.3) or psychiatric hospitals (4.15 ± 2.6). A two-group comparison of the length of inpatient care revealed a significant difference

between those psychiatrists who scored 1-3 (n = 55, 14.22 ± 7.4 wks) and those who scored 7-9 (n = 62, 12.22 ± 4.0) regarding the need to use restraint.

Conclusion: Our results may reflect the current dilemma in Japanese psychiatry wherein psychiatrists must initiate coercive measures to shorten hospitalization stays. This study prompted its subject psychiatrists to consider coercive psychiatric treatments.

Background

There have always been concerns about human rights infringements for coercive psychiatric measures, such as involuntary admission, forced medication, seclusion and/or restraint [1]. Controlled studies have provided no evidence about the validity of such interventions, primarily because ethical considerations make it difficult to perform randomized controlled trials [2,3]. However, such involuntary treatments are indispensable in many clinical practice scenarios, and they are commonly used as strategies to treat patients exhibiting disruptive and violent behaviors [3-7].

The Mental Health Act in Japan was initially passed on May 1, 1950, and was originally called the Mental Hygiene Law. In 1988, the Mental Hygiene Law was revised and renamed the Mental Health Law. In 1995, the current version, the Mental Health and Welfare Law, came into force [8-10]. All psychiatrists practicing in Japan must abide by this law, which provides for the fundamental human rights of people with psychiatric problems.

The Mental Health and Welfare Law defines three types of admission: voluntary hospitalization, hospitalization for medical care and protection, and involuntary hospitalization ordered by a prefectural governor [11]. In Japan, the judicial process does not become involved in decision-making about involuntary hospitalizations. Instead, the Japanese government empowers designated physicians for mental health to be entrusted with safeguarding the rights of subjects with psychiatric conditions. Designated physicians also have the right and duty to initiate and terminate coercive measures such as seclusion and restraint.

In 1998, after the disclosure of human rights violations in some Japanese psychiatric hospitals and in response to pressing social demand, Asai et al. conducted a national survey about involuntary psychiatric treatments and published a detailed report and guidelines the following year [12]. Asai and his collaborators distributed survey sheets to 1,548 hospitals with psychiatric beds and received 1,090 responses (70.4 percent), suggesting an increasing interest in this topic. After this survey and elaborate analysis, official guidelines on restraint and seclusion were published by the Japanese Society of General Hospital Psychiatry's educational committee http://psy.umin.ac.jp/[13]. The issuance of these guidelines deepened clinical psychiatrists' awareness of behavioral restrictions and educated practitioners about the importance of these measures as potential therapeutic strategies in psychiatric emergencies. However, opportunities for studying psychiatric seclusion and restraint are limited when compared to opportunities to study pharmacotherapy or psychotherapy.

The aim of this survey was to learn Japanese psychiatrists' attitudes about emergency interventions for acute psychosis by focusing on involuntary treatments and exploring the possibility of minimizing psychiatric coercive measures.

Methods

Subjects

The subjects of this study were 183 young Japanese psychiatrists. Site investigators were recruited through the Japan Young Psychiatrists Organization's (JYPO; http://jypo.umin.jp/) listserv, and those site investigators in turn encouraged their colleagues to participate in the survey. We provided three options for answering the questionnaire: online, email, or conventional mail. The study authors mailed a questionnaire to site investigators at the collaborating institutes. The site investigators physically distributed the questionnaire to their colleagues or sent an email with the URL and login password for the online questionnaire. All subjects were requested to complete the questionnaire during the survey period, January 1 to February 28, 2009. The purpose of this study was clearly stated on the cover sheet of the questionnaire and answering the questionnaire was considered to be consent. All responders participated in this study without any incentive. Similarly, all authors and subjects involved in this study declared themselves free of any conflict of interest relating to the study.

Questionnaire Contents

The questionnaire consisted of a case vignette and questions in three categories: (1) the use of hospitalization; (2) the length of inpatient care, and (3) the use of seclusion and/or restraint [see Additional file 1]. After reading the case vignette, all respondents were asked to score the need for involuntary hospitalization, identify the type of admission, estimate the length of inpatient care, and the likelihood of prescribing seclusion and/or restraint.

The questionnaires were returned anonymously. However, respondents were asked to provide demographic information regarding their levels of psychiatric experience, the types of facilities in which they worked, the region in which they practice, and whether they were designated mental health physicians. The questionnaire is shown in the Appendix.

Statistical Analysis

Study results were expressed as mean ± SD. Statistical analysis was performed using SPSS 16.0J for Windows (SPSS Japan Inc., Tokyo, Japan). A student's t-test and ANOVA were applied, respectively, for the comparisons of two groups and three or more groups. The statistical significance was set at a p value of less than 0.05.

Results

A total of 183 young psychiatrists answered this study's questionnaire. We collected data from all seven regions in Japan, with relatively higher rates in Hokkaido/Tohoku and Kyushu. Because we used three different methods of data collection (online, email, or conventional mail), it was difficult to calculate a precise total response rate. The response rate for the email attachments and conventional mail was 93.3% (n = 112). However, several factors complicated the response rate calculation for the Internet data collection because some mailing lists used in this study contained a number of invalid addresses. Based on the estimated response rate reported by each site investigator, we estimated the total response rate at approximately 85%. Because of a defect in the questionnaire sheet as distributed during the earliest stage of this study, for 65 out of 183 respondents (35.5 percent) it was impossible to connect scores on a 9-point scale and the psychiatrists' length of clinical experience. The average length of psychiatric experience was 7.49 ± 5.6 (mean ± SD) years (n = 118). The rate of designated physicians was 50.8 percent. Designated mental health physicians had significantly greater clinical experience (11.30 ± 5.2 years, n = 60) as compared to non-designated psychiatrists (3.45 ± 2.2, n = 58). For the type of facility, 103 of the survey participants worked at university hospitals, 36 at general hospitals, and 34 at psychiatric hospitals, and the remaining 10 respondents worked at psychiatric clinics, academic schools, or public health facilities.

The study results were summarized in tables. Almost all respondents (98.9 percent) scored 7 or higher regarding the need for hospitalization, including 162 psychiatrists who scored 9 (88.5 percent) as shown in Table 1. Most respondents scored 7 or higher on a 9-point Likert scale regarding the likelihood of prescribing seclusion (8.43 ± 1.0), whereas the scores regarding prescribing restraint displayed a greater diversity (5.14 ± 2.5).

Table 1: The need for hospitalization, its form and length, and the likelihood of prescribing seclusion and/or restraint.

Necessity of hospitalization	**9 point scale (9 = strongly agree)**	
Overall (n = 183)	8.91 ± 0.3	
Designated physician for mental health (n = 60)	8.85 ± 0.5	p = 0.28
Non-designated physician (n = 58)	8.93 ± 0.3	
Form of admission	Out of 183 respondents	
Voluntary Hospitalization	0	
Medical Care and Protection	77 (42.1%)	
Ordered by Prefectural Governor	104 (56.8%)	
No answer	2 (1.1%)	
Estimated length of hospitalization	Weeks	
Overall (n = 183)	13.53 ± 6.4	
Designated physician for mental health (n = 60)	14.07 ± 7.3	p = 0.31
Non-designated physician (n = 58)	12.88 ± 5.0	
Likelihood of seclusion	9 point scale (9 = strongly agree)	
Overall (n = 182)	8.43 ± 1.0	
Designated physician for mental health (n = 59)	8.51 ± 0.9	p = 0.35
Non-designated physician (n = 58)	8.33 ± 1.2	
Likelihood of restraint	9 point scale (9 = strongly agree)	
Overall (n = 183)	5.14 ± 2.5	
Designated physician for mental health (n = 60)	4.98 ± 2.5	p = 0.37
Non-designated physician (n = 58)	5.40 ± 2.4	

Survey results are expressed with a mean ± SD. P values were calculated with a Student's t-test between the two subgroups. No statistically significant differences were found.

Regarding the likelihood of prescribing restraint, a two-group comparison between designated and non-designated physicians demonstrated no significant difference. However, psychiatrists working at general hospitals did score significantly higher (6.25 ± 2.5) than those who work at university hospitals (5.02 ± 2.3) or psychiatric hospitals (4.15 ± 2.6) as illustrated in Table 2.

We divided the survey respondents into two groups, based on scores regarding the likelihood of prescribing restraint: those psychiatrists who favored restraint (score 7-9) and those who were opposed (score 1-3). Those psychiatrists who favored the use of restraint were found to estimate significantly shorter periods of inpatient care (12.22 ± 4.0) than those professionals who opposed restraint (14.22 ± 7.4).

Discussion

Every psychiatrist must pay careful attention to avoid violating human rights when initiating coercive treatments such as seclusion and restraint. However, these interventions are indispensable in clinical psychiatry, and they are often used as strategies in the treatment of agitated patients.

The Mental Hygiene Law was intended to protect the fundamental human rights of people with mental illness and facilitate their rehabilitation within the community. Since enactment of the law in 1950, all psychiatric medical professionals in Japan have been bound to practice psychiatry with careful consideration to avoid infringing upon human rights. There have been certain calls from a humanitarian viewpoint for the abolition of seclusion and restraint. However, in acute psychiatry, these coercive measures can be useful therapeutic strategies to ensure the safety of psychiatric patients [3-7]. In Japan, judgment regarding the necessity for involuntary psychiatric admission is entrusted to designated mental health physicians. The judicial system never becomes involved in this decision-making process. In order to admit a patient for hospitalization to provide medical care and protection, a designated physician obtains written consent from that patient's guardian [11,14].

Article 29 of the Mental Health and Welfare Law states that if a prefectural governor recognizes that a person who has been examined is diagnosed as mentally disordered and is therefore likely to hurt himself/herself or others unless hospitalized for medical care and protection, the prefectural governor may admit the person to a mental hospital established by the national or prefectural government or a designated hospital. This form of forced hospitalization can be approved only when the person has been examined by at least two designated physicians and the examination results of each physician conclude that the person is mentally disordered and that he or she is likely to hurt himself/herself or others because of a mental disorder unless admitted to a hospital for medical care and protection.

In Japan, there is no uniform residency program in each medical specialty. Instead of standardized training programs, there is a two-tier psychiatric training system in Japan: (1) specialist certification by the Japanese Society of Psychiatry and Neurology; and (2) government designation. To become a designated mental health physician, applicants for designation must have clinical experience exceeding five years, including over three years in general

Table 2: Comparing the likelihood of prescribing restraint and the estimated hospitalization length.

Likelihood of Restraint	9 point scale (9 = strongly agree)	
Overall (n = 183)	5.14 ± 2.5	
Designated mental health physician (n = 60)	4.98 ± 2.5	p = 0.37[1]
Non-designated physician (n = 58)	5.40 ± 2.4	
University hospital (n = 103)	5.02 ± 2.3	
General hospital (n = 36)	6.25 ± 2.5	p = 0.03[2]
Psychiatric hospital (n = 34)	4.15 ± 2.6	p = 0.001[3]
Estimated length of hospitalization	weeks	
Agreed with restraint (score 7-9, n = 62)	12.22 ± 4.0	p = 0.049
Disagreed with restraint (score 1-3, n = 55)	14.22 ± 7.4	

Survey results are expressed with a mean ± SD. p values were calculated using Student's t-test between the two subgroups. Significant differences were found between those psychiatrists practicing in general hospitals and the two other types of hospitals. No significant variation was found between psychiatrists in university and psychiatric hospitals.
Significance of difference between:
[1] Designated mental health physician and Non-designated physician
[2] University hospital and general hospital
[3] General hospital and psychiatric hospital

psychiatry. Designated mental health physician candidates must take a three-day course of lectures and submit eight case reports of involuntary hospitalization in six categories: schizophrenia (three case reports including at least one case in which the patient was admitted by a prefectural gubernatorial order, which is the most coercive type of hospitalization), mood disorder, substance abuse, dementia, organic disorders, and child and adolescent mental health. Thus, the main purpose of this designation system is to thoroughly acquaint psychiatrists with the Mental Health Law and authorize psychiatrists to execute various involuntary interventions based on Japan's strict mental health regulations.

According to the results of the present study, the average score ranking the necessity of hospitalization was 8.91 ± 0.3 on the 9-point Likert scale, with 98.9 percent of respondents scoring a 7 or higher. With regard to the form of admission, opinions were nearly divided in half: 42.1 percent responded that hospitalization for medical care and protection would be most likely, whereas 56.8 percent said an involuntary hospitalization ordered by a prefectural governor would be a likely type of admission. In the case vignette used in this study, Mr. A. brandished a kitchen knife and threatened his neighbors. This behavior may be considered to satisfy the legal requirements for involuntary hospitalization. However, in real life situations, hospitalization for medical care and protection, a less coercive measure, is more commonly suggested. The polarization of the respondents' opinions on this point might be attributable to differences in their interpretations of the case vignette.

There was significant diversity among the respondents' estimations of hospitalization length, which ranged from four weeks (n = 4) to one year (n = 1). The majority of respondents suggested twelve weeks (n = 106), with an average of 13.53 ± 6.4 weeks. Two group comparisons between the designated mental health physicians and the non-designated physicians revealed no statistically significant difference between the two groups' estimations of hospitalization length. Further, no correlations were found between the estimated hospitalization length and the likelihood of prescribing restraint, nor were correlations discovered between the estimated hospitalization length and the length of physicians' psychiatric experience. However, the two group comparisons between psychiatrists who favored restraint and those who opposed it revealed that those practitioners who favored restraint suggested a significantly shorter hospitalization length than those who opposed restraint. We cannot provide a clear explanation for this result. The result might indicate that restraint is considered an outcome of treatments that target earlier improvement in the manifestation of psychiatric symptoms. Hoge et al. reported that most episodes of refusal to take antipsychotic medication by consumers ended with voluntary acceptance of treatment [15]. However, it takes time to persuade patients to take oral medication and often requires additional staff. To ensure minimum coerciveness in psychiatric practice, we need additional studies to explore those factors affecting psychiatrists' decisions about initiating coercive measures.

Psychiatrists in other countries may consider a three-month hospitalization to be somewhat excessively long. However, it is noteworthy that Japan has been criticized for its lengthy hospitalization periods for schizophrenic patients [11]. When considering this national mental health care backdrop, the three-month hospitalization suggested in this study certainly reflects the recent improvements in Japanese psychiatrists' awareness about shortening hospital stay durations. In the treatment case presented, the patient lives alone and has no prior history of psychotic episodes. Unfortunately, Japan still suffers from a lack of social resources enabling people with mental disorders to live within their communities. Further measures are needed to shorten the length of hospital stays.

For employing seclusion versus restraint, the score for the likelihood of prescribing seclusion showed a high concurrence rate among the respondents, with an average of 8.43 ± 1.0 on a 9-point scale. Alternatively, the score for the likelihood of prescribing restraint ranged from 1 to 9, with an average of 5.14 ± 2.5. In Japan, seclusion in a room with a certain amount of space and equipped with a bathroom is considered less restrictive than restraint. At a previously held international workshop on seclusion and restraint that we organized, we realized through discussions with psychiatrists from other countries that cultural backgrounds would influence psychiatrists' opinions about behavioral restrictions [16]. For instance, when the Czech Republic became a target of criticism because of their use of a cage bed--a bed surrounded by a metal cage used to restrain a patient--the Czechs explained that in the Czech Republic the use of a "net bed" was considered more humane than other restraint techniques, such as straps, isolation rooms, or even strong medication. It is important to understand that differences in psychiatric opinions may be due to differences between cultural backgrounds [17].

When comparing scores for estimated hospitalization lengths, according to the types of hospitals where physicians work, those who work at general hospitals suggested a significantly longer period than those who work at university hospitals or psychiatric hospitals. One reason for this result could be explained by the psychiatric departments in most general hospitals being understaffed while having a higher percentage of patients requiring restraint,

for example, people who are sent to the emergency room with an altered level of consciousness or delirium patients with comorbid physical conditions. Another reason could be that there are increasing numbers of patients with behavioral and psychological symptoms of dementia (BPSD) resulting from the rapid aging of the Japanese population. Yet another reason for expecting a longer hospitalization period at general hospitals might be the nurses' working environment. It has been reported that training nurses is effective in decreasing the number of behavioral restrictions at hospitals [18,19]. However, certain nursing system characteristics in the psychiatric wards of many general hospitals could be hindering this effect. For instance, nurses in general hospitals are routinely transferred to different wards after a certain period of time and therefore are likely to be less experienced, tending to resign sooner because of their workload.

As for limitations of this survey, the questionnaire was sent to the subjects with a brief description of an imaginary case rather than a real patient. The subjects of this study represent only a subset of psychiatrist in Japan. The latest data provided by the Japanese Ministry of Health, Labor and Welfare reports that the total number of psychiatrists was 12,474, accounting for 4.49% of all medical doctors in 2006 (on-line database of JMHLW; http://www.mhlw.go.jp/toukei/). The number of doctors under the age of 40 was 93,409 in 2006. Considering these data, we estimated the number of young psychiatrists as 4,194. Thus, the subjects of this study account for 4.36% of all young Japanese psychiatrists. Similarly, the number of designated physicians for mental health was 11,791 in 2006. Our sample included only 0.5% of those designated physicians, indicating limited representation. In regard to the 9-point scale used in this study, a 5 score indicates neither agreement nor disagreement on a 9-point Likert scale (with 9 being the highest possible score) and the significance of the deviation from the mean of 5 remains controversial. Therefore, it is difficult for us to draw firm conclusions.

Conclusion

In recent years, many studies have been conducted on psychiatric seclusion and restraint, especially in Europe [20-22]. It has been reported that some programs have succeeded in reducing restraint [23,24]. A previous study revealed that experiencing coercion during admission negatively affected patients' attitudes toward treatment and adherence to medication [25]. We believe that psychiatrists early in their careers should consider how to minimize the use of behavioral restrictions. It is feasible that early training determines the subsequent clinical custom of each psychiatrist. Going forth into clinical duties with this in mind will no doubt shorten the hours of seclusion and restraint for current and future patients.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The members of Coercive Treatment in Psychiatry Study Group of Japan Young Psychiatrists Organization (MT, KS, KU, DF, YZ, NH, HT, NY, SS) designed the study protocol and collected data in collaboration with site investigators (TK, WN, YW, TS, SK). All authors had full access to the data. MT performed the statistical analysis and drafted the manuscript. All authors have read and approved the final manuscript.

Additional material

Additional file 1

Questionnaire. The questionnaire with case vignette used in this study.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1752-4458-3-20-S1.DOC]

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Regional dopamine synthesis in patients with schizophrenia using L-[β-^{11}C]DOPA PET

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ABSTRACT

The dopamine hypothesis has been the most widely known theory concerning schizophrenia. However, the exact mechanism including presynaptic dopaminergic activity and its relationship with symptom severity still remains to be revealed. We measured presynaptic dopamine synthesis using positron emission tomography (PET) with L-[β-^{11}C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as k_i values, were obtained using a graphical method, and the occipital cortex was used as reference region. Regions of interest were placed on the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). We found significantly higher k_i values in patients than in controls in the left caudate nucleus, but not in the other regions. The k_i values in the thalamus exhibited a significant positive correlation with the PANSS total scores. Furthermore, a significant positive correlation was observed between the PANSS positive subscale scores and k_i values in the right temporal cortex. Patients with schizophrenia showed higher dopamine synthesis in the left caudate nucleus, and dopaminergic transmission in the thalamus and right temporal cortex might be implicated in the expression of symptoms in schizophrenia.

1. Introduction

Positron emission tomography (PET) has allowed us to investigate the dopamine hypothesis in living human brain. Since there is no ideal animal model of schizophrenia, PET investigation is still the most useful method for investigating neurotransmission in patients. As for postsynaptic dopaminergic receptors, several studies have investigated striatal (Farde et al., 1990; Nordström et al., 1995; Wong et al., 1986) and extrastriatal (Suhara et al., 2002; Yasuno et al., 2004) D_2 receptor (D_2R) binding by the use of PET. Although studies investigating D_2R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D_2R binding have repeatedly reported its reduction in the anterior cingulate cortex (Suhara et al., 2002) and the thalamus in schizophrenia (Talvik et al., 2003; Yasuno et al., 2004). Regarding intrasynaptic function, striatal dopamine release was reported to be enhanced in schizophrenia (Breier et al., 1997; Laruelle et al., 1996). On the other hand, many studies did not find any change in dopamine transporter binding in the striatum of schizophrenia (Laakso et al., 2000;

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Laruelle et al., 2000; Schmitt et al., 2005; Yang et al., 2004). These findings suggest that patients with schizophrenia may have elevated presynaptic dopamine synthesis, and investigations on presynaptic dopaminergic function in extrastriatal regions might be critical for providing an understanding of the pathophysiology of schizophrenia.

Radiolabeled L-DOPA, a precursor of dopamine, has been used to investigate presynaptic dopamine synthesis. L-DOPA is transported through the blood–brain barrier (BBB), taken up by presynaptic monoaminergic neurons, and metabolized to dopamine by aromatic amino acid decarboxylase (AADC). Previous studies on the dopamine synthesis of schizophrenia used 6-[^{18}F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashef et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[β-^{11}C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[^{18}F]fluoro-L-DOPA, which is widely used in schizophrenia research, indicated elevated dopamine synthesis (Hietala et al., 1995, 1999; Lindström et al., 1999; McGowan et al., 2004; Reith et al., 1994), elevated dopamine turnover (Kumakura et al., 2007), only higher variability (Dao-Castellana et al., 1997), and even reduced synthesis (Elkashef et al., 2000) in the striatum.

The 3-O-methyl metabolite of L-DOPA crossing the BBB can reportedly cause an error in quantification of the dopamine synthesis rate (Dhawan et al., 1996; Melega et al., 1990; Wahl et al., 1994). However, 3-O-methylation of L-[β-^{11}C]DOPA does not take place readily and rapidly when compared with 6-[^{18}F]fluoro-L-DOPA (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Recently, we evaluated the accuracy of quantitative analyses of L-[β-^{11}C]DOPA PET studies (Ito et al., 2006). In the current study, we investigated regional dopamine synthesis and its relationship with the severity of positive and negative symptoms in patients with schizophrenia using L-[β-^{11}C]DOPA.

2. Methods

2.1. Participants

Fourteen (8 males and 6 females) drug-naïve and 4 (2 males and 2 females) 3-month drug-free patients (35.6±7.4 years, mean±SD) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia or schizophreniform disorder were recruited from the outpatient units of university hospitals, their affiliated psychiatric hospitals, and a mental clinic. On the day of the PET study, the diagnosis was re-evaluated by 3 experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The severity of psychotic symptoms was also evaluated by the same 3 psychiatrists with the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Igarashi et al., 1998). Each interview was conducted by 2 of 3 authors (S.N., F.Y., M.O.) and one other psychiatrist. Patients with schizophreniform disorder (2 males and 2 females) at the time of the PET study were followed up for at least 6 months from onset, confirming that they eventually met the criteria of schizophrenia. Twenty (10 males and 10 females) healthy volunteers (35.1±9.5 years) were recruited as controls through public notices. All the subjects were examined by physicians to obtain data concerning their educational background as well as current and past medical problems, and family history by unstructured interview and a general questionnaire. Handedness was assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971). The control subjects were matched with the patients for age, gender, education, and handedness. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. The demographic characteristics of all participants are shown in Table 1. Exclusion criteria of patients and controls were as follows: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse including alcohol; (3) previous episodes of mood disorder. One patient was excluded because of a large cyst in the cerebellum (data not shown).

After giving explanation of the study, written informed consent was obtained from all patients and control subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET study

All the participants were instructed to fast for 4 h before PET scan in order to avoid the influence of the plasma concentration of neutral amino acid (NAA) on the L-[β-^{11}C]DOPA uptake rate. A PET scanner (ECAT EXACT HR, CTI-Siemens, Knoxville, TN), providing 63 planes with an axial field of view of 15.5-cm, was used. A head fixation device (Fixster, Stockholm Sweden) was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Data acquisition was performed in 3-dimensional mode with the interplane septa retracted. A bolus of 331.5 to 401.8 MBq (373.0±14.1 MBq, mean±SD) of L-[β-^{11}C]DOPA with specific radioactivities (9.9–156.4 GBq/μmol) was injected intravenously via the antecubital vein and flushed rapidly with 20 mL of saline. Dynamic scans were performed for 64 min immediately after the injection. The scanning sequence consisted of seven 1-min frames, five 2-min frames, four 3-min frames, and seven 5-min frames. All emission scan data were reconstructed with a Hanning filter with a cutoff frequency of 0.4 (final in-plane resolution: 7.5 mm full width at half maximum).

Table 1
Demographic and clinical characteristics of patients with schizophrenia and normal controls

	Controls (n=20)	Patients (n=18)
Gender, M/F	10/10	10/8
Age, y, mean±SD	35.1±9.5	35.6±7.4
Range	20–55	20–52
Medication, no. naïve (M/F)/free (M/F)		14 (8/6)/4 (2/2)
Handedness, no. right/left	20/0	18/0
Education, y, mean (range)	15.1 (12–9)	14.1 (9–16)
No. of smokers (M/F)	4 (4/0)	6 (4/2)
Duration of illness, mo, mean (range)		26.4 (1–120)
PANSS		
Whole score		
Mean±SD		79.2±21.4
Range		46–124
Subscales		
Positive (mean±SD)		22.6±7.3
Negative (mean±SD)		17.1±6.5
General psycho (mean±SD)		39.6±11.0

Table 2
k_i values of each ROI in patients with schizophrenia and normal controls

Region	L/R	Controls	Patients	ANCOVA#	
		(n=20)	(n=18)	F	p
Parahippocampus	L	4.54±1.13	4.91±1.45	0.704	0.407
	R	4.76±1.11	4.47±1.29	0.528	0.472
Temporal cortex	L	1.92±0.99	1.98±0.81	0.041	0.842
	R	1.86±0.83	1.92±0.87	0.037	0.849
Prefrontal cortex	L	1.31±0.73	1.22±0.64	0.324	0.573
	R	1.35±0.73	1.35±0.57	0	1.000
Thalamus	L	3.55±1.60	3.19±1.72	0.549	0.463
	R	3.11±1.45	3.09±1.54	0.001	0.970
Putamen	L	15.52±2.04	15.76±2.14	0.139	0.711
	R	15.39±2.31	14.90±3.01	0.329	0.570
Caudate	L	12.89±2.68	14.66±2.38	4.409	0.043*
	R	13.71±2.74	13.59±2.09	0.026	0.872
Anterior cingulate	L	2.74±1.33	3.05±1.50	0.445	0.509
	R	3.24±1.73	3.00±1.13	0.288	0.595

Dopamine synthesis rates, expressed as $k_i \times 1000$, were presented as mean± standard deviation.
#: Analysis of covariance with age as covariate (df=1, 35).
L indicates left and R indicates right. The symbol * represents $p<0.05$.

2.3. Magnetic resonance images

For each participant, a structure magnetic resonance (MR) image was obtained. All MR imaging studies were performed with a 1.5-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, TE: 9.2 ms; repetition time, TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256×256; slice thickness: 1 mm).

2.4. Data analysis

All MR images were coregistered to the PET summation images of all frames using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROIs) were drawn on the coregistered MR images, referring to the human brain atlas (Mai et al., 1997), and then transferred to the PET images. ROIs were defined for the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. The ROIs were set on both left and right sides of the brain and those values were independently evaluated. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

The overall uptake rate constant k_i of L-[β-^{11}C]DOPA, which indicates the net dopamine synthesis rate, was determined for each ROI by the graphical plot analysis method developed by Gjedde and Patlak (Gjedde, 1982; Ito et al., 2006; Patlak and Blasberg, 1985). k_i values can be estimated by simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F_{t>t^*}$$

where C_i is the total radioactivity concentration in a brain region that can be measured by PET, C_i' is the total radioactivity concentration in the reference brain region with no irreversible compartments, and t^* is the equilibrium time of the compartment for unchanged radioligand in the brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after the time t^*, yields a straight line with the slope k_i and intercept F. In the present study, the occipital cortex was used as reference region (Ito et al., 2006). A range of equilibrium time t^* of 31.5 to 61.5 min was used.

ROI analyses were independently performed by 3 researchers who were blinded to the diagnoses. The intraclass correlation coefficient across all ROIs was 0.976 (McGraw and Wong, 1996), considered as excellent. In order to reduce variance, the k_i values by one researcher that most frequently showed medium values among those obtained by the 3 researchers were used for the following analyses.

2.5. Statistical analysis

Demographic variables were compared by independent sample t-test or chi-square test. Differences in the k_i values for each of the 7 × 2 brain regions between patients and controls were evaluated by one-way univariate analyses of covariance with age as a covariate, since an effect of age on k_i values has been reported (Ota et al., 2006). Pearson's correlation coefficients were calculated between the PANSS scores and k_i values. A significance level of $p<0.05$ (two-tailed) was used both in the comparison analyses between groups and in the correlation analyses.

3. Results

3.1. Demographic data

The demographic data of schizophrenia patients and controls are shown in Table 1. There were no significant differences between patients and controls in terms of age, gender, education, handedness, and the injected dose and

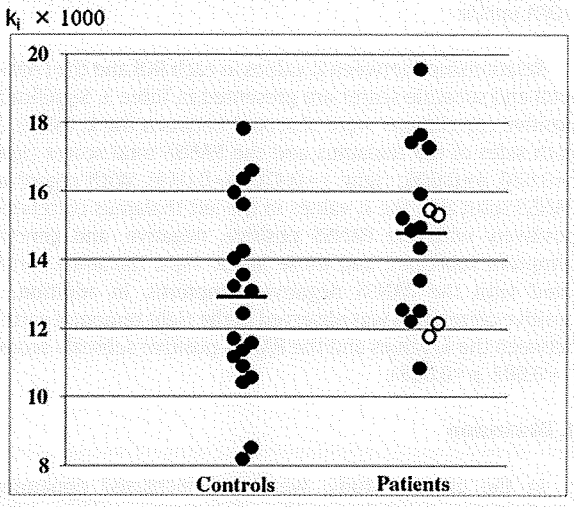

Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those of drug-free patients.

Table 3
Correlations between k_i values of each ROI and PANSS scores in schizophrenia

Region	L/R	Total scores		Positive symptoms		Negative symptoms		General symptoms	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Parahippocampus	L	−0.003	0.992	0.045	0.859	0.080	0.752	−0.083	0.745
	R	0.284	0.253	0.288	0.246	0.197	0.434	0.245	0.328
Temporal cortex	L	−0.088	0.728	0.133	0.598	−0.049	0.848	−0.232	0.355
	R	0.465	0.052	0.603	0.008*	0.242	0.334	0.361	0.141
Prefrontal cortex	L	0.380	0.120	0.288	0.246	0.339	0.168	0.346	0.160
	R	0.407	0.094	0.302	0.082	0.457	0.057	0.320	0.196
Thalamus	L	0.620	0.006*	0.490	0.039*	0.504	0.033*	0.589	0.010*
	R	0.470	0.049*	0.378	0.122	0.492	0.038*	0.372	0.129
Putamen	L	0.247	0.323	0.177	0.482	0.342	0.165	0.160	0.525
	R	0.359	0.143	0.327	0.186	0.407	0.094	0.240	0.338
Caudate	L	0.287	0.323	0.294	0.236	0.319	0.197	0.174	0.490
	R	−0.183	0.468	−0.223	0.375	0.021	0.935	−0.220	0.380
Anterior cingulate	L	−0.270	0.120	0.202	0.421	−0.418	0.085	−0.412	0.089
	R	0.355	0.149	0.421	0.082	0.303	0.222	0.231	0.357

L indicates left and R indicates right.
The symbol * represents $p<0.05$.

specific radioactivity of L-[β-^{11}C]DOPA. The duration of illness and the PANSS scores are also shown in Table 1.

3.2. Regional L-[β-^{11}C]DOPA uptake in schizophrenia and control subjects

Univariate analysis of covariance revealed no significant interaction between group and age in any of the regions, and a significant group difference in k_i values only for the left caudate between normal controls and schizophrenia patients was observed ($df=1, 35$, $F=4.409$, $p=0.043$; Table 2 and Fig. 1). In addition, no significant difference was observed in the k_i values between antipsychotic drug-naïve and drug-free patients in any of the regions.

Furthermore, there was no significant correlation between the k_i values in any ROIs and the duration of illness in patients.

3.3. Severity of positive and negative symptoms and L-[β-^{11}C] DOPA uptake

Relationships between k_i values in each ROI and the PANSS total and subscale scores are presented in Table 3. Significant positive correlations were observed between the k_i values in both sides of the thalamus and the PANSS total scores (left: $r=0.620$, $p=0.006$; right: $r=0.470$, $p=0.049$). With regard to PANSS subscales, the k_i values in the left thalamus correlated positively with the PANSS positive, negative, and general symptom subscales, and those in the right thalamus correlated with the PANSS negative symptoms. In addition, a positive correlation was observed in the right temporal cortex between the k_i values and the PANSS positive subscale scores ($r=0.603$, $p=0.008$).

4. Discussion

In the present study, we found increased dopamine synthesis in the left caudate nucleus in patients with schizophrenia compared to normal controls. In addition, we observed a significant correlation between regional dopamine synthesis in the thalamus as well as in the right temporal cortex and symptom severity in patients.

Most of the previous studies with 6-[^{18}F]fluoro-L-DOPA have reported elevated dopamine synthesis mainly in the striatum of patients with schizophrenia (Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994), whereas decreased (Elkashef et al., 2000) or only greater variability (Dao-Castellana et al., 1997) have also been reported in this region. There are some plausible explanations for these inconsistent results. First, the participants with schizophrenia in these studies were not homogeneous. For example, one study investigated heterogeneous patients with psychosis (Reith et al., 1994), while the other studies included patients with schizoaffective disorder (Hietala et al., 1995, 1999). Furthermore, schizophrenia patients on antipsychotic medication participated in two of the PET studies (Elkashef et al., 2000; McGowan et al., 2004). Interestingly, a study on only unmedicated schizophrenia patients showed only greater variability in k_i values compared with normal controls (Dao-Castellana et al., 1997). Second, the differences between 6-[^{18}F] fluoro-L-DOPA and L-[β-^{11}C]DOPA in terms of 3-O-methyl metabolite of L-DOPA crossing the BBB might also result in such inconsistency (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Kumakura et al. reported a method to reduce this problem with metabolites and demonstrated that catabolism and elimination of 6-[^{18}F]fluoro-L-DOPA was elevated nearly 2-fold in the striatum in 8 patients with schizophrenia as compared to that in 15 age-matched control subjects. They concluded that not only the synthesis but also the turnover of radiolabeled dopamine was increased in patients with schizophrenia (Kumakura et al., 2007).

Lindström et al. (1999) investigated unmedicated schizophrenia patients using L-[β-^{11}C]DOPA and found increased dopamine synthesis in the striatum and medial prefrontal cortex, while we observed elevated dopamine synthesis only in the left caudate. As for differences between the two studies, however, the patients in the study of Lindström et al. had relatively more severe psychotic symptoms (Clinical Global Impression ≥4) than our patients. In addition, our patients were mostly outpatients, and thus, such a difference in the demographic of patients might be responsible for the difference in results. In addition, the caudate nucleus might be more important than the putamen in the pathophysiology

of schizophrenia because the caudate has extensive interconnections from the limbic and cortical areas, which play crucial roles in the regulation of cognition and emotion compared to the putamen (Parent, 1990). Further, lateralization to the left of the caudate is consistent with the reports by Hietala et al. (1995, 1999).

With regard to the relationships with symptoms, in our patients, presynaptic dopamine synthesis in the thalamus was positively correlated with overall symptom severity, although that in the right thalamus was correlated only with PANSS negative scores, besides the PANSS total scores; in addition, dopamine synthesis in the right temporal cortex was positively correlated with positive symptoms. The thalamus has been repeatedly reported to be engaged in the pathophysiology of schizophrenia (Clinton and Meador-Woodruff, 2004; Takahashi et al., 2006). Previous neuroimaging studies have shown altered thalamic perfusion and metabolism (Andreasen et al., 1997; Buchsbaum et al., 1996; Clark et al., 2001; Hazlett et al., 1999, 2004; Kim et al., 2000; Mitelman et al., 2005; Resnick et al., 1988) and decreased dopamine D_2 receptor availability in the thalamus in patients with schizophrenia (Buchsbaum et al., 2006; Talvik et al., 2003, 2006; Yasuno et al., 2004). The thalamus is reported to have a pivotal role in the processing and integrating of sensory information related to emotional and cognitive functions (Clinton and Meador-Woodruff, 2004), and it has also been suggested to have sensory gating function (Carlsson et al., 2000; Takahashi et al., 2006). Further, elevated dopamine transmission in the thalamus was reported to disrupt sensory gating function (Young et al., 1995). Impaired gating function could contribute to both positive and negative symptoms by the inability to automatically "gate out" much redundant and unessential information, leading to irrelevant thought and fragmentation of mind and behavior in schizophrenia (Braff et al., 1999). Additionally, one study with 6-[^{18}F]fluoro-L-DOPA examined before and after 5 weeks of haloperidol treatment for schizophrenia demonstrated that the thalamus was the only structure in which the change of dopamine synthesis was related to improvement in negative symptoms (Gründer et al., 2003). Thus, dopaminergic regulation in the thalamus might be associated with positive and negative symptoms in schizophrenia. However, the contribution of different roles of each side of the thalamus to diverse symptom dimensions remains unclear.

In terms of the correlation between dopamine synthesis in the right temporal cortex and the PANSS scale, our data suggested that higher dopamine synthesis in the right temporal cortex might be associated with the expression of positive symptoms in patients with schizophrenia. Previous functional MRI studies have demonstrated the involvement of the right temporal cortex in some of the positive symptoms such as auditory hallucination (Shergill et al., 2000; Woodruff et al., 1997) and formal thought disorder (Kircher et al., 2002) in schizophrenia. On the other hand, although previous PET (Buchsbaum et al., 2006) and SPECT (Tuppurainen et al., 2003) studies have suggested decreased dopamine D_2R binding in the right temporal cortex, no significant correlation was found between the binding and positive symptoms. Furthermore, no study has demonstrated the relationship between presynaptic dopamine synthesis in the right temporal cortex and positive symptoms.

There are several limitations in the present study. First, smoking is regarded as a confounding factor in the estimation of k_i values (Salokangas et al., 2000), and some of our participants were smokers, although the smoking rate of the patients was only slightly higher than that of the normal controls (33% for patients and 20% for controls). Second, our patients consisted of both males and females, although we selected age- and gender-matched control subjects. Laakso et al. (2002) indicated gender differences in striatal dopamine synthesis with the use of 6-[^{18}F]fluoro-L-DOPA PET. However, we did not find such differences in our subjects (data not shown). Nonetheless, since gender differences have been suggested in schizophrenia (Salem and Kring, 1998), this issue should be addressed in future studies. Finally, although our sample size is hitherto the largest among reported studies on dopamine synthesis in schizophrenia, the current study may still not have enough power. Our results of both comparison and correlation analyses were significant only when uncorrected for multiple comparisons, and the failure to observe significant correlations with symptoms in other regions might be due to a type II error. Therefore, further investigations using still larger samples are required.

5. Conclusion

We measured the dopamine synthesis rate in patients with schizophrenia and normal control subjects by using PET with L-[β-^{11}C]DOPA. Patients had higher dopamine synthesis in the left caudate nucleus than controls, which was in line with the results of most previous studies that indicated an increase in dopamine synthesis in the striatum. Moreover, correlation analyses between k_i values and symptoms suggested that dopamine synthesis in the thalamus and right temporal cortex might be implicated in the pathophysiology of schizophrenia. There is little evidence concerning extrastriatal presynaptic dopaminergic functions of schizophrenia in vivo. Further studies are required to better understand the presynaptic dopaminergic functions of schizophrenia.

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Contributors

S. Nozaki, F. Yasuno, A. Takano, and T. Suhara designed the study and wrote the protocol. S. Nozaki, M. Kato, F. Yasuno, M. Ota, A. Otsuka, and Y. Okubo recruited the patients and made psychiatric evaluations. S. Nozaki, H. Takano, M. Okumura, R. Arakawa, R. Matsumoto, and Y. Fujimura participated in the data analysis. S. Nozaki wrote the first draft of the manuscript. S. Nozaki, M. Kato, H. Takano, H. Takahashi, H. Ito, H. Kashima and T. Suhara had discussions and corrected the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors have no conflict of interest.

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Behavioral/Systems/Cognitive

Effects of the Antipsychotic Risperidone on Dopamine Synthesis in Human Brain Measured by Positron Emission Tomography with L-[β-^{11}C]DOPA: A Stabilizing Effect for Dopaminergic Neurotransmission?

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Effects of antipsychotic drugs have widely been considered to be mediated by blockade of postsynaptic dopamine D_2 receptors. Effects of antipsychotics on presynaptic functions of dopaminergic neurotransmission might also be related to therapeutic effects of antipsychotics. To investigate the effects of antipsychotics on presynaptic functions of dopaminergic neurotransmission in relation with occupancy of dopamine D_2 receptors, changes in dopamine synthesis capacity by antipsychotics and occupancy of dopamine D_2 receptors were measured by positron emission tomography (PET) in healthy men. PET studies using [^{11}C]raclopride and L-[β-^{11}C]DOPA were performed under resting condition and oral administration of single dose of the antipsychotic drug risperidone on separate days. Although occupancy of dopamine D_2 receptors corresponding dose of risperidone was observed, the changes in dopamine synthesis capacity by the administration of risperidone were not significant, nor was the relation between the occupancy of dopamine D_2 receptors and these changes. A significant negative correlation was observed between the baseline dopamine synthesis capacity and the changes in dopamine synthesis capacity by risperidone, indicating that this antipsychotic can be assumed to stabilize the dopamine synthesis capacity. The therapeutic effects of risperidone in schizophrenia might be related to such stabilizing effects on dopaminergic neurotransmission responsivity.

Introduction

Effects of antipsychotic drugs have widely been considered to be mediated by blockade of postsynaptic dopamine D_2 receptors (Carlsson and Lindqvist, 1963; Creese et al., 1976; Seeman et al., 1976). This hypothesis has been supported by positron emission tomography (PET) studies to determine the occupancy of dopamine D_2 receptors in schizophrenia patients treated with first-generation antipsychotics, e.g., haloperidol (Farde et al., 1988; Baron et al., 1989) and second-generation antipsychotics, e.g., risperidone (Nyberg et al., 1993).

Effects of antipsychotics on presynaptic functions of dopaminergic neurotransmission might also be related to the therapeutic effects of antipsychotics. It has been reported that antipsychotic drugs, chlorpromazine and haloperidol, increased dopamine metabolites in mouse brain tissue (Carlsson and Lindqvist, 1963; O'Keeffe et al., 1970), and also that risperidone and clozapine increased dopamine release in rat brain (Hertel et al., 1996). Increases and decreases in the activity of aromatic L-amino acid decarboxylase (AADC) by antagonists and agonists of dopamine D_2 receptors were also observed in rat brain tissue, respectively (Zhu et al., 1992, 1993). The regional activity of AADC in brain indicating the dopamine synthesis capacity can be estimated using radiolabeled L-DOPA (Gjedde et al., 1991). Significant increases and decreases in dopamine synthesis capacities by antagonists and agonists of dopamine D_2 receptors were observed in animal studies using [^{3}H]DOPA, L-[β-^{11}C]DOPA, or 6-[^{18}F]fluoro-L-DOPA, respectively (Cumming et al., 1997; Torstenson et al., 1998; Danielsen et al., 2001). These findings indicate that pharmacological effects on dopaminergic autoreceptors might cause changes in the presynaptic dopamine synthesis capacity (Carlsson and Lindqvist, 1963).

Effects of antipsychotics on the dopamine synthesis capacity in brain have been investigated in human subjects. A significant increase in dopamine synthesis capacity after acute administration of antipsychotic drug haloperidol was observed using PET with 6-[^{18}F]fluoro-L-DOPA in healthy human subjects (Vernaleken et al., 2006). On the other hand, a significant decrease in dopamine synthesis capacity after chronic administration of haloperidol was observed using 6-[^{18}F]fluoro-L-DOPA in patients with schizophrenia (Gründer et al., 2003). A significant in-

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crease in the plasma concentration of homovanillic acid after acute administration of antipsychotics, haloperidol or fluphenazine, was observed in patients with schizophrenia, indicating an increase in dopamine turnover (Davila et al., 1988; Pickar et al., 1988). During chronic administration, a significant decrease in the plasma concentration of homovanillic acid was also observed (Davila et al., 1988; Pickar et al., 1988). However, the effects of antipsychotics on the dopamine synthesis capacity have not been investigated in relation to the occupancy of dopamine D_2 receptors in human subjects.

Recently, we have validated quantitative analyses in L-[β-^{11}C]DOPA PET studies (Ito et al., 2006, 2007). In the present study, to elucidate changes in dopamine synthesis capacity by antipsychotics in relation to the occupancy of dopamine D_2 receptors, dopamine D_2 receptor bindings and dopamine synthesis capacities at resting condition and after oral administration of a single dose of the antipsychotic drug risperidone were measured in the same human subjects by PET with [^{11}C]raclopride and L-[β-^{11}C]DOPA, respectively.

Materials and Methods

Subjects. The study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan. Twelve healthy men (21–29 years of age, 24.3 ± 2.9 years [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 according to interview.

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 the PET measurements.

PET studies were performed under resting condition (baseline study) and oral administration of risperidone (drug challenge study) on separate days. The interval between the 2 studies was 7 d in 10 subjects, and 14 d in 2 subjects. In each study, both PET scans with [^{11}C]raclopride and L-[β-^{11}C]DOPA were performed sequentially. After intravenous rapid bolus injection of [^{11}C]raclopride, dynamic PET scanning was performed for 60 min. After 1 h from the end of the [^{11}C]raclopride PET measurement, dynamic PET scanning was performed for 89 min after intravenous rapid bolus injection of L-[b-^{11}C]DOPA. 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 220–230 MBq and 342–395 MBq in the baseline studies, and 205–274 MBq and 344–388 MBq in the drug challenge studies for [^{11}C]raclopride and L-[β-^{11}C]DOPA, respectively. The specific radioactivity was 168–517 GBq/μmol and 26–88 GBq/μmol in the baseline studies, and 162–535 GBq/μmol and 39–90 GBq/μmol in the drug challenge studies 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 Corp.). 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 work (Ito et al., 2006).

Table 1. Dose of risperidone and ranges of occupancy of dopamine D_2 receptors

	Occupancy (%)	
Dose of risperidone (mg)	Putamen	Caudate
0.5	39–46%	33–44%
1.0	48–52%	48–60%
1.5	61–69%	63–71%
2.0	71–75%	75–79%

In the drug challenge studies, risperidone at 0.5–2.0 mg was orally administrated 2 h before the start of PET scanning with [^{11}C]raclopride. The dose of risperidone was 0.5 mg in 3 subjects, 1.0 mg in 3 subjects, 1.5 mg in 3 subjects, and 2.0 mg in 3 subjects. To estimate the plasma concentration of risperidone and its active metabolite (9-hydroxy-risperidone), venous blood sampling was performed at the start and end of each PET scan. The plasma concentrations of risperidone and 9-hydroxy-risperidone were determined by validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method. Since risperidone and 9-hydroxy-risperidone have similar binding profiles to neuroreceptors (Leysen et al., 1994), the sum of their plasma concentrations was used as the plasma concentration of the antipsychotic drug in the present study.

All MR imaging studies were performed with a 1.5-tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, 9.2 ms; repetition time, 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, putamen, caudate head, 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. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time. In-house software was used to draw ROIs.

Calculation of occupancy of dopamine D_2 receptors. For both PET studies with [^{11}C]raclopride, the binding potential (BP_{ND}) was calculated by the reference tissue model method (Lammertsma et al., 1996; Lammertsma and Hume, 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 non-displaceable 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 ⊗ denotes the convolution integral. 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 a reference region. The occupancy of dopamine D_2 receptors by risperidone was calculated as follows:

$$\text{Occupancy (\%)} = 100 \cdot BP_{ND(baseline)} - BP_{ND(drug)})/BP_{ND(baseline)},$$

where $BP_{ND(baseline)}$ is the BP_{ND} value in the baseline study, and $BP_{ND(drug)}$ is the BP_{ND} value in the drug challenge study.

Calculation of dopamine synthesis capacity. The uptake rate constant for L-[β-^{11}C]DOPA indicating the dopamine synthesis capacity was estimated by graphical analysis (Patlak and Blasberg, 1985; Gjedde, 1988; Hartvig et al.,

1991), which allows for the calculation of the uptake rate constant k_i using time-activity data in a reference brain region with no irreversible binding. The k_i values can be estimated by using simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \cdot \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F \qquad t < t^*,$$

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_i 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 aromatic L-amino acid decarboxylase activity (Lloyd and Hornykiewicz, 1972). The range of equilibrium time t^* of 29–89 min was used (Ito et al., 2006, 2007). The percentage change in k_i by oral administration of risperidone was calculated as follows:

$$\% \text{ change} = 100 \cdot (k_{i(drug)} - k_{i(baseline)})/k_{i(baseline)},$$

where $k_{i(baseline)}$ is the k_i value in the baseline study, and $k_{i(drug)}$ is the k_i value in the drug challenge study.

Results

The ranges of occupancy of dopamine D_2 receptors in the striatum for each dose of risperidone measured by PET with [^{11}C]raclopride are given in Table 1. The occupancies of dopamine D_2 receptors ranged from 39% to 75% in the putamen and from 33% to 79% in the caudate. The sums of the plasma concentrations of risperidone and 9-hydroxy-risperidone during [^{11}C]raclopride and L-[β-^{11}C]DOPA PET studies, averaged between the start and end of each scanning, ranged from 3.8 to 23.1 ng/ml (12.2 ± 6.6 ng/ml, mean ± SD) and from 2.6 to 19.5 ng/ml (10.5 ± 5.8 ng/ml), respectively.

The uptake rate constant k_i of L-[β-^{11}C]DOPA in the striatum indicating the dopamine synthesis capacity for baseline and drug challenge study results are shown in Figure 1. The k_i values were 0.0136 ± 0.0017 min^{-1} and 0.0142 ± 0.0010 min^{-1} (mean ± SD) in the putamen and 0.0121 ± 0.0018 min^{-1} and 0.0125 ± 0.0015 min^{-1} in the caudate for baseline and drug challenge studies, respectively. No significant differences in k_i were observed between the two studies. Weighted sums of the natural neutral amino acids (NAAs) in plasma were 1251 ± 198 nmol/ml for the baseline studies and 1207 ± 199 nmol/ml (mean ± SD) for the drug challenge studies. No significant differences in values were observed between the two studies.

The relations between the occupancy of dopamine D_2 receptors and the percentage change in k_i by drug challenge are

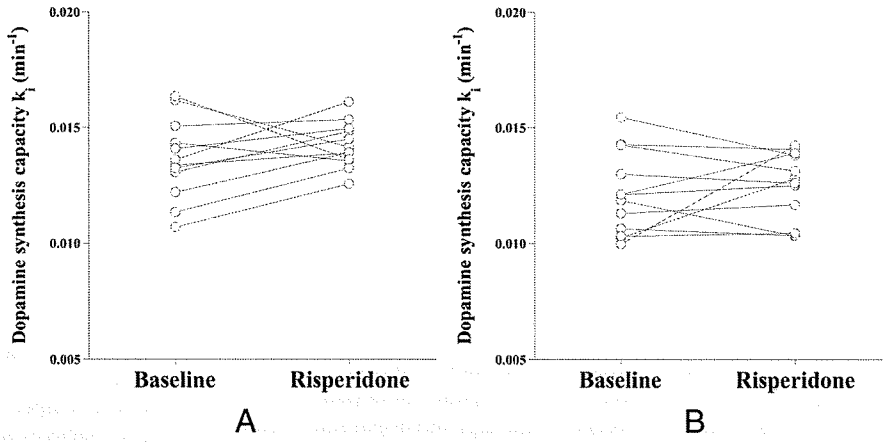

Figure 1. The uptake rate constant k_i indicating the dopamine synthesis capacity for the baseline study and drug challenge study with risperidone in the putamen (*A*) and caudate (*B*).

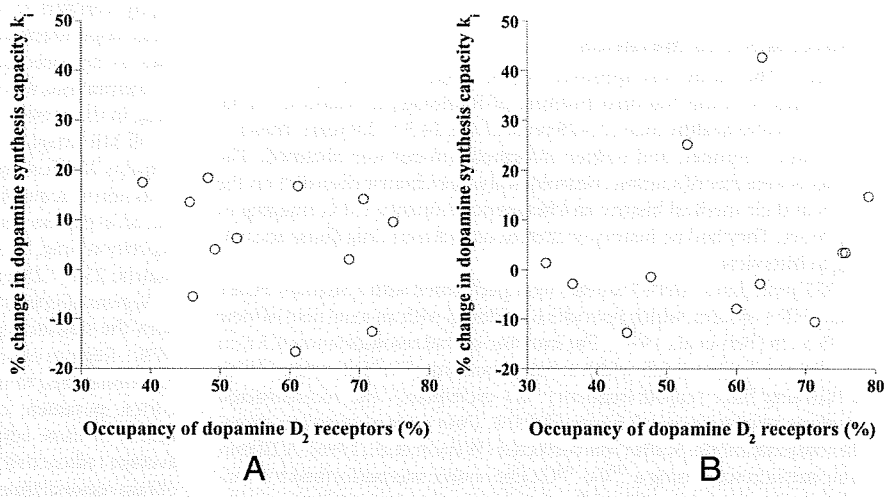

Figure 2. The relations between the occupancy of dopamine D_2 receptors and the percentage change in k_i by drug challenge with risperidone in the putamen (*A*) and caudate (*B*).

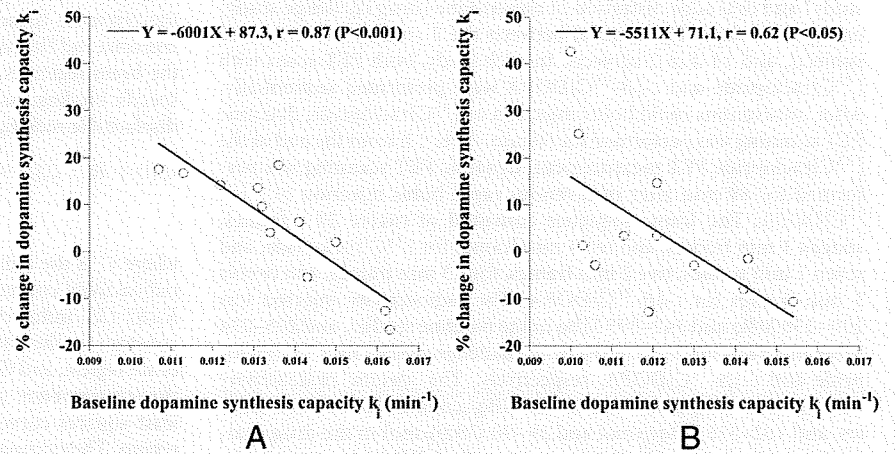

Figure 3. The relations between k_i in the baseline study and the percentage changes in k_i by drug challenge with risperidone in the putamen (*A*) and caudate (*B*).

shown in Figure 2. No significant correlations were observed. The relations between k_i in the baseline study and percentage change in k_i by the drug challenge are shown in Figure 3. Significant negative correlations were observed (putamen: $p < 0.001$, caudate: $p < 0.05$).

Discussion

Effects of antipsychotics on presynaptic dopamine synthesis might be caused by pharmacological activity on dopaminergic autoreceptors (Carlsson and Lindqvist, 1963). Although occupancy of dopamine D_2 receptors corresponding to the dose of risperidone was observed, no significant changes in the dopamine synthesis capacity k_i by administration of risperidone were observed in the present study. Furthermore, there were no significant correlations between the occupancy of dopamine D_2 receptors and changes in dopamine synthesis capacity k_i by risperidone. No significant changes in the dopamine synthesis capacity after acute administration of risperidone in healthy human subjects were also reported using 6-[^{18}F]-L-*m*-tyrosine (Mamo et al., 2004). On the other hand, a significant increase in the dopamine synthesis capacity measured using 6-[^{18}F]fluoro-L-DOPA and a significant increase in the plasma concentration of homovanillic acid have been observed after acute administration of antipsychotics, haloperidol or fluphenazine, in healthy human subjects (Vernaleken et al., 2006) and patients with schizophrenia (Davila et al., 1988; Pickar et al., 1988), respectively. The discrepancy between the present and previous results might have resulted from the use of different antipsychotics. However, in rat brain, it has been reported that risperidone and clozapine also increased dopamine release (Hertel et al., 1996). Another reason for this discrepancy might due to differences in the radiotracers used. However, in animal studies with [^{3}H]DOPA, L-[β-^{11}C]DOPA, or 6-[^{18}F]fluoro-L-DOPA, significant increases and decreases in dopamine synthesis capacities by antagonists and agonists of dopamine D_2 receptors, respectively, have been observed (Cumming et al., 1997; Torstenson et al., 1998; Danielsen et al., 2001).

In the present study, significant negative correlations were observed between the baseline dopamine synthesis capacity k_i and the percentage changes in the dopamine synthesis capacity by risperidone. This indicates that the increase and decrease in dopamine synthesis capacity by administration of risperidone are observed in subjects with low and high baseline dopamine synthesis capacity, respectively, and the degrees of increase and decrease in dopamine synthesis capacity are greater as the baseline dopamine synthesis capacities are smaller and larger, respectively. Negative correlations between baseline cerebral 6-[^{18}F]fluoro-L-DOPA utilization and change in 6-[^{18}F]fluoro-L-DOPA storage capacity by haloperidol challenge have also been observed in healthy human subjects (Vernaleken et al., 2008), corresponding to our present results. In addition, the coefficients of variation of dopamine synthesis capacity k_i were smaller in studies with the administration of risperidone than in baseline studies. Thus, the antipsychotic drug risperidone can be assumed to stabilize the dopamine synthesis capacity. The concept of phasic and tonic dopamine release with relation to the modulation of dopaminergic neurotransmission has been proposed, and abnormal responsivity in both phasic and tonic dopamine release in schizophrenia has been considered (Grace, 1991). The therapeutic effects of risperidone might be related to stabilizing effects on such dopaminergic responsivity. In addition, it has been reported that an antipsychotic drug, clozapine, normalized dopamine turnover in the primate phencyclidine model, indicating that the effects of clozapine in schizophrenia might be related to the restoration of dopamine tone (Elsworth et al., 2008). In this study, only an acute intervention was performed on healthy subjects, and therefore, the chronic effects of antipsychotics on patients with schizophrenia should be investigated in future.

It has been reported that the working memory and learning functions were correlated with the baseline dopamine synthesis capacity (Cools et al., 2008, 2009). Further studies to investigate the effects of antipsychotics on such higher brain functions in relation with changes in dopamine synthesis capacity should be considered (Vernaleken et al., 2008).

Serotonin 5-HT_{2A} receptor antagonists have been reported to modulate endogenous dopamine release (Pehek et al., 2001), and to reduce extrapyramidal side effects (Balsara et al., 1979; Korsgaard et al., 1985; Hicks, 1990). Risperidone is an antagonist for dopamine D_2 receptors and serotonin 5-HT_{2A} receptors with high affinity (Leysen et al., 1994), and it has been reported to modulate endogenous dopamine release. These findings indicate that changes in the dopamine synthesis capacity by administration of risperidone might be due to not only pharmacological effects on dopaminergic autoreceptors, but also on serotonin 5-HT_{2A} receptors. Thus, the stabilizing effects of risperidone on the dopamine synthesis level might also be related to its antagonism toward serotonin 5-HT_{2A} receptors. To elucidate this, further studies based on the same design using a selective antagonist for dopamine D_2 receptors, such as sulpiride, should be considered. In addition, a new antipsychotic drug aripiprazole that is a partial agonist to dopamine D_2 receptors has recently been used for treatment of schizophrenia (Mamo et al., 2007). Further studies to investigate the effects of aripiprazole on dopamine synthesis capacity should also be considered.

In conclusion, dopamine D_2 receptor bindings and dopamine synthesis capacities at resting condition and after oral administration of a single dose of the antipsychotic drug risperidone were measured in the same human subjects. Although occupancy of dopamine D_2 receptors corresponding to the dose of risperidone was observed, no significant changes in dopamine synthesis capacity by administration of risperidone were observed. It was also noted that there was no significant correlation between occupancy of dopamine D_2 receptors and changes in dopamine synthesis capacity by risperidone. On the other hand, a significant negative correlation was observed between the baseline dopamine synthesis capacity and the changes in dopamine synthesis capacity by risperidone. This indicates that the antipsychotic drug risperidone can be considered to stabilize the dopamine synthesis capacity. This suggests that the therapeutic effects of risperidone in schizophrenia might be related to the stabilizing effects on dopaminergic neurotransmission responsivity.

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