Fig. 5. Areas showing significant correlations of BP_{ND} values between [^{11}C]DASB and [^{11}C]WAY100635 in intrasubject comparisons. (a) insula, (b) anterior cingulate, (c) posterior cingulate, (d) base side of frontal cortex, (e) lateral temporal cortex, (f) parietal cortex.

regions, they tend to positively correlate with each other except the occipital cortex. This finding could reflect innervation of serotonergic fibers in those regions.

5-HTT-rich region

Brain stem. High binding to 5-HTT was observed in large areas of the midbrain, and it continuously

extended to the thalamus; this finding indicated rich distribution in these regions. In contrast, moderate binding to 5-HT_{1A} receptors was observed only in the dorsal and medial raphe, with this distribution indicating that 5-HT_{1A} receptor exists only in these regions of the midbrain (the sagittal section, middle column in the bottom row in Figure 2; the transverse sections, the first to fourth columns in the second row from the bottom; further, refer to the volume of interest 6 in Figure 1, which represents the raphe nuclei). These distribution patterns of 5-HTT and 5-HT_{1A} were consistent with those observed in previous human postmortem autoradiography studies (Hall et al., 1997; Varnas et al., 2004). In the present study, however, 5-HT_{1A} binding was not very high as compared with that in other areas (Table II). For example, the mean BP_{ND} value in the dorsal raphe was approximately one-third of that in the hippocampus, which exhibited the highest value of all regions examined. Further, in a detailed human autoradiography study with [^{3}H]WAY100635, binding to the dorsal raphe was highest (140 pmol/g tissue), followed by the hippocampus (123 pmol/g tissue). However, this discrepancy may be a result of the limited spatial resolution of the PET scanner, resulting in excessive spillover from the raphe and other small structures.

Subcortical regions. In the striatum (putamen and caudate) and globus pallidus, relatively high levels of binding to 5-HTT were observed. In contrast, 5-HT_{1A} receptor binding was very low or absent in the caudate nucleus and globus pallidus, while a low level of binding was found in the putamen. However, postmortem autoradiography studies showed very low levels of binding in the putamen, similar to those in the caudate and globus pallidus (Hall et al., 1997; Varnas et al., 2004); the high BP_{ND} values in the putamen may be attributed to spillover from the insula, which exhibits a very high level of 5-HT_{1A} binding.

The level of 5-HTT binding in the thalamus was the second highest among all brain regions, after the dorsal raphe nucleus; further, there was no marked difference in 5-HTT distribution among the subregions of the thalamus. These findings were similar to those of a previous human postmortem study (Varnas et al., 2004). On the other hand, the level of binding to the 5-HT_{1A} receptor was very low in the thalamus, although a little binding was observed in its medial parts regions (Table II and Figs. 2–4); this finding was similar to those of previous autoradiography studies showing much less or no binding in these regions (Hall et al., 1997; Varnas et al., 2004).

5-HT_{1A} receptor-rich region

Cerebral neocortex. Relatively high binding to 5-HT_{1A} and low binding to 5-HTT were observed in the neocortical regions. The 5-HT_{1A} receptor was widely distributed in the cerebral cortex but sparsely in the occipital cortex. The distribution of 5-HTT was very low in the neocortical regions as compared with other brain regions, but was found to be homogeneous among the cortical regions (Figs. 2–4, Table II). These findings were consistent with those of previous postmortem autoradiography studies (Hall et al., 1997; Laruelle et al., 1988; Varnas et al., 2004).

Limbic regions. In the hippocampal regions that include the parahippocampus, hippocampus, and uncus (amygdala), highest binding to 5-HT_{1A} and moderate binding to 5-HTT were observed (Figs. 2–4, Table II). Postmortem autoradiography studies in humans revealed that the highest binding to 5-HT_{1A} was observed particularly over the CA1 field in the hippocampus (Hall et al., 1997; Varnas et al., 2004). In contrast, binding to 5-HTT was higher in the uncus as compared to other hippocampal regions, a finding in agreement with a previous postmortem study (Varnas et al., 2004).

Within the cingulate cortex, both 5-HTT and 5-HT_{1A} binding can be described in descending order as follows: ventral (subcallosal) cingulate > anterior cingulate > posterior cingulate (Table II and Figs 2 and 3). In particular, the ventral cingulate is thought to be involved in the regulation of emotions and has been repeatedly reported to be associated with depression (Drevets et al., 2008; Seminowicz et al., 2004).

Very high 5-HT_{1A} binding and intermediate 5-HTT binding were observed in the insula. These distributions are in accordance with those found in previous human postmortem autoradiography studies (Varnas et al., 2004), although BP_{ND} values in the insula can be affected by spillover from the striatum, which exhibits high levels of 5-HTT binding.

Our findings together suggest that the limbic regions, including the hippocampal area, cingulate cortex, and insula, are relatively rich in serotonergic innervation. Thus, serotonergic transmission in these regions might play a pivotal role in modulating emotion and cognition.

Intraindividual relationship between the binding of both [^{11}C]DASB and [^{11}C]WAY100635 in the same region of the brain

With respect to the intraindividual relationship between regional 5-HTT and 5-HT_{1A} distribution, we found significant negative linear correlations between the binding of [^{11}C]DASB and [^{11}C]WAY100635 in the insula; anterior and posterior cingulate; and lateral temporal, frontal base, and parietal cortices. This result suggests that serotonergic transmission might be modulated by a cooperative relationship between 5-HTT and 5-HT_{1A}.

There have been only a few reports on pre- and postsynaptic serotonergic functions in individuals. In a study of 12 men, Lundberg et al. (2007) showed a positive linear correlation between 5-HTT and 5-HT$_{1A}$ binding in the raphe nuclei and hippocampal complex using [^{11}C]MADAM and [^{11}C]WAY100635, respectively; however, a positive linear correlation was not observed in the frontal cortex. Another study that examined gender differences in binding using [^{11}C]MADAM and [^{11}C]WAY100635 also reported an interrelationship between 5-HTT and 5-HT$_{1A}$ receptors (Jovanovic et al., 2008). They found a significant positive correlation between BP$_{ND}$ of 5-HTT and 5-HT$_{1A}$ receptors in the hippocampus of eight women, whereas no significant correlation was observed in seven men. The discrepancy between their results and ours could be attributed to the use of different 5-HTT radiotracers, sample size, and subjects' background. In particular, the age range of subjects in the study by Lundberg et al. was wider than ours, and different degrees of atrophy can cause positive correlation in BP$_{ND}$ between 5-HTT and 5-HT$_{1A}$ receptor. This is because older subjects are likely to have more brain atrophy, because of which both BP$_{ND}$ values are lower than those of young subjects. Our results suggest that subjects exhibiting higher 5-HTT binding are likely to have less 5-HT$_{1A}$ receptor binding and vice versa. One possible interpretation of this intersubject difference is that individuals with higher 5-HT synthesis and release show a decrease in the 5-HT$_{1A}$ receptor function to dampen the transmission at the postsynaptic site and an increase in 5-HTT function in order to reuptake more 5-HT at the presynaptic site, whereas individuals with lower 5-HT synthesis and release show an increase in the 5-HT$_{1A}$ receptor function and a decrease in 5-HTT function to reuptake less 5-HT; that is, pre- and postsynaptic 5-HT functions are modulated cooperatively to compensate the overall 5-HT transmission. However, these studies were done under resting condition, and therefore challenge study designs using drugs or stress may help to better understand the relationship between pre- and postsynaptic functions.

Limitation

There are several limitations to the current study. First, the two PET studies were not always performed on the same day. Good reproducibility for both ligands (Kim et al., 2006; Rabiner et al., 2002), however, has been demonstrated, and it has been shown that the endogenous 5-HT level has no direct effect on binding (Rabiner et al., 2002; Talbot et al., 2005); hence, it is unlikely that the endogenous level affected the results. Second, the sample size was small, especially for a correlation study between pre- and postsynaptic functions, and our study should necessarily be

regarded as a preliminary one. Third, we focused only on 5-HTT and 5-HT$_{1A}$ receptors because they reportedly play pivotal roles in serotonergic functions. However, there are more than 10 receptor systems in the brain that affect serotonergic transmission. In addition, monoamine oxidase as well as 5-HTT are known to control the 5-HT concentration in the synapse (Nestler et al., 2008). Finally, the current study includes only young men, and we should expand it to women and individuals of a wider range of ages. Such a database will be helpful even for clinical studies on depression and anxiety disorders, since these disorders are known to show different prevalence and clinical features depending on gender and age (Fernandez et al., 1995; Gorman, 2006; Pigott, 1999). The physiological differences in the 5-HT system based on gender and age might explain the characteristics of depression and anxiety disorders.

In summary, we constructed a normal database to elucidate regional distributions of 5-HT$_{1A}$ and 5-HTT binding. The neuroanatomy of the 5-HT$_{1A}$ and 5-HTT serotonergic systems was discussed mostly by comparing our findings with those of previous postmortem studies. Furthermore, we explored the linear negative correlation between pre- and postsynaptic functions in certain parts of the brain. The results obtained indicate the involvement of a cooperative or complementary process in serotonergic transmission. Further studies are required to elucidate the modulation of 5-HT transmission in neuropsychiatric disorders and to clarify the various serotonergic systems involving pre- and postsynaptic functions in different regions of the brain.

REFERENCES

Brust P, Hesse S, Muller U, Szabo Z. 2006. Neuroimaging of the serotonin transporter. Curr Psychiatry Rev 2:111–149.
Cooper JR, Bloom FE, Roth RH. 2002. The biochemical basis of neuropharmacology, 8th ed. New York, USA: Oxford University Press.
Diksic M, Young SN. 2001. Study of the brain serotonergic system with labeled alpha-methyl-L-tryptophan. J Neurochem 78:1185–1200.
Drevets WC, Savitz J, Trimble M. 2008. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr 13:663–681.
Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, Mathis C. 2007. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nucl Med Biol 34:865–877.
Fernandez F, Levy JK, Lachar BL, Small GW. 1995. The management of depression and anxiety in the elderly. J Clin Psychiatry 56(Suppl 2):20–29.
Gorman JM. 2006. Gender differences in depression and response to psychotropic medication. Gend Med 3:93–109.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. 1997. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 6:279–287.

Gunn RN, Sargent PA, Bench CJ, Rabiner EA, Osman S, Pike VW, Hume SP, Grasby PM, Lammertsma AA. 1998. Tracer kinetic modeling of the 5-HT1A receptor ligand [carbonyl-^{11}C]WAY-100635 for PET. Neuroimage 8:426–440.

Hall H, Lundkvist C, Halldin C, Farde L, Pike VW, McCarron JA, Fletcher A, Cliffe IA, Barf T, Wikstrom H, Sedvall G. 1997. Autoradiographic localization of 5-HT$_{1A}$ receptors in the post-mortem human brain using [^{3}H]WAY-100635 and [^{11}C]way-100635. Brain Res 745:96–108.

Hoyer D, Hannon JP, Martin GR. 2002. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 71:533–554.

Hoyer D, Pazos A, Probst A, Palacios JM. 1986. Serotonin receptors in the human brain. I. Characterization and autoradiographic localization of 5-HT$_{1A}$ recognition sites. Apparent absence of 5-HT$_{1B}$ recognition sites. Brain Res 376:85–96.

Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE. 2003. Linearized reference tissue parametric imaging methods: application to [^{11}C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 23:1096–1112.

Ichise M, Toyama H, Innis RB, Carson RE. 2002. Strategies to improve neuroreceptor parameter estimation by linear regression analysis. J Cereb Blood Flow Metab 22:1271–1281.

Innis RB, Cunningham VJ, Delforge J, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539.

Ito H, Halldin C, Farde L. 1999. Localization of 5-HT$_{1A}$ receptors in the living human brain using [carbonyl-^{11}C]WAY-100635: PET with anatomic standardization technique. J Nucl Med 40:102–109.

Ito H, Takahashi H, Arakawa R, Takano H, Suhara T. 2008. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. Neuroimage 39:555–565.

Jovanovic H, Lundberg J, Karlsson P, Cerin A, Saijo T, Varrone A, Halldin C, Nordstrrom A-L. 2008. Sex differences in the serotonin 1A receptor and serotonin transporter binding in the human brain measured by PET. Neuroimage 39:1408–1419.

Kim JS, Ichise M, Sangare J, Innis RB. 2006. PET imaging of serotonin transporters with [^{11}C]DASB: test-retest reproducibility using a multilinear reference tissue parametric imaging method. J Nucl Med 47:208–214.

Kish SJ, Furukawa Y, Chang LJ, Tong J, Ginovart N, Wilson A, Houle S, Meyer JH. 2005. Regional distribution of serotonin transporter protein in postmortem human brain: is the cerebellum a SERT-free brain region? Nucl Med Biol 32:123–128.

Kitson SL. 2007. 5-hydroxytryptamine (5-HT) receptor ligands. Curr Pharm Des 13:2621–2637.

Kumar JSD, Mann JJ. 2007. PET tracers for 5-HT(1A) receptors and uses thereof. Drug Discov Today 12:748–756.

Lammertsma AA, Hume SP. 1996. Simplified reference tissue model for PET receptor studies. Neuroimage 4:153–158.

Laruelle M, Vanisberg MA, Maloteaux JM. 1988. Regional and subcellular localization in human brain of [^{3}H]paroxetine binding, a marker of serotonin uptake sites. Biol Psychiatry 24:299–309.

Lundberg J, Borg J, Halldin C, Farde L. 2007. A PET study on regional coexpression of 5-HT$_{1A}$ receptors and 5-HTT in the human brain. Psychopharmacology 195:425–433.

Lundquist P, Blomquist G, Hartvig P, Hagberg GE, Torstenson R, Hammarlund-Udenaes M, Langstrom B. 2006. Validation studies on the 5-hydroxy-L-[beta-^{11}C]-tryptophan/PET method for probing the decarboxylase step in serotonin synthesis. Synapse 59:521–531.

Marner L, Gillings N, Comley RA, Baare WF, Rabiner EA, Wilson AA, Houle S, Hasselbalch SG, Svarer C, Gunn RN, Laruelle M, Knudsen GM. 2009. Kinetic modeling of ^{11}C-SB207145 binding to 5-HT$_4$ receptors in the human brain in vivo. J Nucl Med 50:900–908.

Meyer JH. 2007. Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. J Psychiatry Neurosci 32:86–102.

Moresco RM, Matarrese M, Fazio F. 2006. PET and SPET molecular imaging: Focus on serotonin system. Curr Top Med Chem 6:2027–2034.

Nestler E, Hyman S, Malenka R. 2008. Molecular neuropharmacology: A foundation for clinical neuroscience, 2nd ed. New York, USA: McGraw-Hill Professional.

Pazos A, Probst A, Palacios JM. 1987. Serotonin receptors in the human brain. III. Autoradiographic mapping of serotonin-1 receptors. Neuroscience 21:97–122.

Pigott TA. 1999. Gender differences in the epidemiology and treatment of anxiety disorders. J Clin Psychiatry 60(Suppl 18):4–15.

Rabiner EA, Messa C, Sargent PA, Husted-Kjaer K, Montgomery A, Lawrence AD, Bench CJ, Gunn RN, Cowen P, Grasby PM. 2002. A database of [^{11}C]WAY-100635 binding to 5-HT$_{1A}$ receptors in normal male volunteers: Normative data and relationship to methodological, demographic, physiological, and behavioral variables. Neuroimage 15:620–632.

Savitz J, Lucki I, Drevets WC. 2009. 5-HT$_{1A}$ receptor function in major depressive disorder. Prog Neurobiol 88:17–31.

Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, Rafi-Tari S. 2004. Limbic-frontal circuitry in major depression: A path modeling metanalysis. Neuroimage 22:409–418.

Stockmeier CA. 2003. Involvement of serotonin in depression: Evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. J Psychiatr Res 37:357–373.

Suhara T, Sudo Y, Yoshida K, Okubo Y, Fukuda H, Obata T, Yoshikawa K, Suzuki K, Sasaki Y. 1998. Lung as reservoir for antidepressants in pharmacokinetic drug interactions. Lancet 351:332–335.

Talbot PS, Frankle WG, Hwang DR, Huang Y, Suckow RF, Slifstein M, Abi-Dargham A, Laruelle M. 2005. Effects of reduced endogenous 5-HT on the in vivo binding of the serotonin transporter radioligand ^{11}C-DASB in healthy humans. Synapse 55:164–175.

Varnas K, Halldin C, Hall H. 2004. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. Hum Brain Mapp 22:246–260.

ORIGINAL INVESTIGATION

Dopamine D₂ receptor occupancy by perospirone: a positron emission tomography study in patients with schizophrenia and healthy subjects

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Abstract

Rationale Perospirone is a novel second-generation antipsychotic drug with high affinity to dopamine D_2 receptor and short half-life of plasma concentration. There has been no investigation of dopamine D_2 receptor occupancy in patients with schizophrenia and the time course of occupancy by antipsychotics with perospirone-like properties.

Objective We investigated dopamine D_2 receptor occupancy by perospirone in patients with schizophrenia and the time course of occupancy in healthy subjects.

Materials and methods Six patients with schizophrenia taking 16–48 mg/day of perospirone participated. Positron emission tomography (PET) scans using [^{11}C]FLB457 were performed on each subject, and dopamine D_2 receptor occupancies were calculated. Moreover, baseline and three serial PET using [^{11}C]raclopride were performed at 1.5, 8, and 25.5 h after administration of a single dose of 16 mg of perospirone on four healthy male subjects, and occupancy was calculated for each scan.

Results Dopamine D_2 receptor occupancy in the temporal cortex of patients ranged from 39.6% to 83.8%. Especially, occupancy in two patients who took 16 mg of perospirone 2.5 h before PET was over 70%. Mean occupancy in the striatum of healthy subjects was 74.8% at 1.5 h, 60.1% at 8 h, and 31.9% at 25.5 h after administration.

Conclusion Sixteen milligrams of perospirone caused over 70% dopamine D_2 receptor occupancy near its peak level, and then occupancy dropped to about half after 22 h. The time courses of receptor occupancy and plasma concentration were quite different. This single dosage may be sufficient for the treatment of schizophrenia and might be useful as a new dosing schedule choice.

Keywords Dopamine D_2 receptor occupancy ·
Perospirone · Positron emission tomography ·
Schizophrenia · Time course

Introduction

Perospirone is a novel second-generation antipsychotic drug used in Japan (Onrust and McClellan 2001). This drug shows high affinity to dopamine D_2 receptor (K_i= 1.77 nM) and serotonin 5-HT$_2$ receptor (K_i=0.06 nM; Takahashi et al. 1998), and its plasma concentration has a short half-life ($T_{1/2}$=1.9 h; Yasui-Furukori et al. 2004). A previous positron emission tomography (PET) study using [^{11}C]raclopride and [^{11}C]NMSP in healthy subjects with single 8 mg of perospirone showed blockage of both dopamine D_2 receptor and serotonin 5-HT$_2$ receptor (Sekine et al. 2006), but the optimal dose of perospirone in patients with schizophrenia has not been investigated.

Kapur et al. (2000b) reported that transient high dopamine D_2 receptor occupancy by quetiapine showed clinical effects for patients with schizophrenia. They suggested that this transient occupancy was related to "atypical" features of second-generation antipsychotics

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with low affinity for dopamine D_2 receptor (Kapur and Seeman 2001). Plasma pharmacokinetics and affinity for receptor were considered to affect the time course of receptor occupancy (Kapur and Seeman 2001; Takano et al. 2004). However, the time course of receptor occupancy by antipsychotics with high affinity for dopamine D_2 receptor and a short half-life of plasma concentration has not been investigated.

In this study, we investigated dopamine D_2 receptor occupancy by several doses of perospirone in patients with schizophrenia. Moreover, we investigated the time course of dopamine D_2 receptor occupancy by perospirone with serial PET scanning in healthy subjects.

Materials and methods

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

Patient study

Subjects and study protocol

Six patients aged 26–44 years (34.9±7.1, mean ± SD), diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders-IV criteria, participated in this study (Table 1). Exclusion criteria were current or past substance abuse, brain tumor or vascular disease, and history of severe head injury or epilepsy. Subjects with severe liver or renal dysfunction, or having undergone electroconvulsive therapy within 90 days prior to this study were also excluded. The patients had been taking fixed dosages of perospirone for more than 2 weeks before this study. Doses of perospirone were 16 mg/day in one patient, 24 mg/day in two patients, and 48 mg/day in three patients. The interval between the last administration of perospirone

and PET scan was from 2.5 to 17.5 h. Clinical symptoms were assessed by positive and negative symptom scale (PANSS). Venous blood samples were taken before and after PET scanning to measure the plasma concentration of perospirone and ID-15036, an active metabolite of perospirone (hydroxyperospirone). The average values of pre- and post-PET scanning were used.

PET procedure

A PET scanner system, ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA), was used for all subjects. A head fixation device was used to minimize head movement. Before the dynamic scan, a transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source. The dynamic PET scan was performed for 90 min after intravenous bolus injection of 204.0–225.0 MBq (218.5± 7.7 MBq, mean ± SD) of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 129.6–219.4 MBq/nmol (175.4±34.3 MBq/nmol, mean ± SD). Magnetic resonance images of the brain were acquired with 1.5 Tesla magnetic resonance imaging (MRI), Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images at 1-mm slices were obtained.

Data analysis

All emission scan data were reconstructed with a Hanning filter. Regions-of-interest (ROIs) were defined for the temporal cortex and cerebellar cortex. ROIs were drawn manually on PET images with reference to the individual MR images. The values of ROIs for right and left sides were averaged. Binding potential (BP_{ND}), defined as the specific binding compared to nondisplaceable uptake, of dopamine D_2 receptor in the temporal cortex was calculated using a three-parameter simplified reference tissue model (SRTM; Innis et al. 2007; Lammertsma and Hume 1996). The cerebellum was used as reference tissue because of its negligible density of dopamine D_2 receptors (Suhara et al. 1999).

Table 1 Patient characteristics, plasma concentration, and dopamine D_2 receptor occupancy

Number	Age (year)	Sex	PANSS	Dose (mg/day)	Interval: last dose–PET (h)	Last dose (mg)	Plasma concentration		Receptor occupancy (%)
							Perospirone (ng/ml)	ID-15036 (ng/ml)	
1	38	M	59	16	2.5	16	4.5	23.3	83.8
2	30	F	69	24	7.5	8	0.6	3.05	61.8
3	44	F	62	24	9.0	8	0	0.75	39.6
4	26	M	81	48	2.5	8	1.25	8.45	60.8
5	30	F	46	48	2.5	16	0.25	8.35	70.1
6	42	F	80	48	17.5	32	0.85	2.1	65.0

Receptor occupancy of perospirone is expressed as follows: Occupancy(%) $= \left(BP_{baseline} - BP_{drug}\right)/BP_{baseline} \times$ 100, where $BP_{baseline}$ is BP_{ND} in the drug-free state, and BP_{drug} is BP_{ND} after administration of the drug. Mean BP_{ND} of age-matched ten normal male subjects (age range 25–43 years; 34.8 ± 6.7 years, mean ± SD) measured by the same procedure as for the patients was used as BP_{base} because of the lack of individual baseline BP_{ND}.

The relationship between receptor occupancy and plasma concentration of antipsychotic drug can be expressed as follows: Occupancy(%) $= C/(C + EC_{50}) \times 100$, where C is the plasma concentration of perospirone or ID-15036, and EC_{50} is the concentration required to induce 50% occupancy.

Measurement of plasma concentration of perospirone

Plasma concentrations of perospirone and ID-15036 were determined using a validated high performance liquid chromatography method (Yasui-Furukori et al. 2003; MP-Technopharma Corporation, Fukuoka, Japan). The lower limit of quantification was 0.1 ng/ml for both perospirone and ID-15036.

Healthy subject study

Subjects and study protocol

Four healthy male subjects aged 22–32 years (26.8 ± 4.1, mean ± SD) participated in the other part of this study. None had a history of psychiatric, neurological, or somatic disorders. None had taken any medication for at least 2 weeks prior to this study. The baseline PET scan was performed within 2 weeks before taking perospirone. All subjects took a single dose of 16 mg of perospirone, and then three serial PET scans were performed at 1.5, 8, and 25.5 h after its administration. Venous blood samples were taken 11 times, at 0.5, 1.0, 1.5, 2.5, 3.5, 5.0, 6.5, 8.0, 9.0, 25.5, and 26.5 h after perospirone administration, to measure the plasma concentrations of perospirone and ID-15036.

PET procedure

A PET scanner system, ECAT EXACT HR+, was used for all subjects. A head fixation device was used to minimize head movement. Before the dynamic scan, a transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source. The dynamic PET scan was performed for 60 min after intravenous bolus injection of 179.6–246.8 MBq (217.0 ± 16.5 MBq, mean ± SD) of [^{11}C] raclopride. The specific radioactivity of [^{11}C]raclopride was 138.0–320.9 MBq/nmol (235.4 ± 65.8 MBq/nmol, mean ± SD). T1-weighted images at 1-mm slices of the brain were acquired with 1.5 Tesla MRI, Gyroscan NT.

Data analysis

All emission scan data were reconstructed with a Hanning filter. ROIs were defined for the striatum and cerebellar cortex and were drawn manually on the PET images with reference to individual MR images. The values of ROIs for right and left sides were averaged. BP_{ND} of dopamine D_2 receptor in the striatum was calculated using SRTM. The cerebellum was used as reference tissue. Receptor occupancy was calculated using the individual BP_{ND} values of baseline and drug administration.

Results

Patient study

Dopamine D_2 receptor occupancy of patients with schizophrenia in the temporal cortex ranged from 39.6% to 83.8% (Table 1). Plasma concentrations of perospirone and ID-15036 ranged from 0 to 4.5 and 0.75 to 23.3 ng/ml, respectively. The plasma concentrations of perospirone and ID-15036 were fitted curvilinearly to the dopamine D_2 receptor occupancy (Fig. 1a, b). Estimated EC_{50} values of perospirone and ID-15036 were 0.31 and 1.90 ng/ml, respectively. The total PANSS score ranged from 46 to 81, and the average score of all patients was 66.2 ± 13.4.
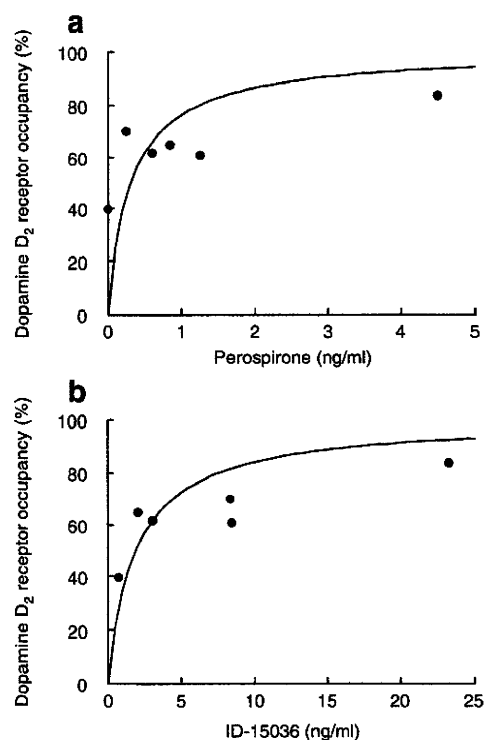

Fig. 1 Relationship between dopamine D_2 receptor occupancy and perospirone (a) and ID-15036 (b) in the patients study

Healthy subject study

Mean dopamine D_2 receptor occupancies in the striatum were 74.8±8.0% at 1.5 h, 60.1±5.6% at 8 h, and 31.9±6.4% at 25.5 h after administration of 16 mg of perospirone in healthy subjects (Fig. 2). The mean plasma concentrations of both perospirone and ID-15036 reached a peak at 1 h after administration, then rapidly decreased, and were not detectable at 25.5 h after (Fig. 3a, b). Estimated half-lives of plasma concentrations of perospirone and ID-15036 were 2.2 and 1.9 h, respectively. No subject complained of severe side effects such as extrapyramidal symptoms or sleepiness.

Discussion

Clinical dose of perospirone

A previous study reported that dopamine D_2 receptor occupancy using [^{11}C]raclopride was 44.4% with 8 mg of perospirone at 1 h post-administration (Sekine et al. 2006). PET studies have suggested that more than 70% dopamine D_2 receptor occupancy is necessary for antipsychotic effect and that 80% occupancy causes extrapyramidal symptoms (Farde et al. 1992; Kapur et al. 2000a; Nordstrom et al. 1993). Two patients (numbers 1 and 5) administered perospirone at 16 mg 2.5 h before PET scanning showed over 70% occupancy. On the other hand, one patient (number 4) taking 8 mg did not reach 70% occupancy in spite of a short interval between the last administration and PET scan. In healthy subjects, a peak of about 75% occupancy was also obtained with 16 mg of perospirone. Although some patients could be maintained at less than 70% occupancy, 16 mg of perospirone seems to be the necessary dose for achieving antipsychotic effect. The plasma concentrations of perospirone and ID-15036 inducing 70% occupancy (EC_{70}) were 0.72 and 4.43 ng/ml, respectively. Side effects could not be evaluated in this study because some patients were taking
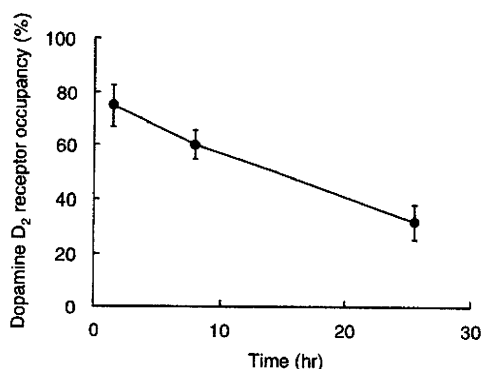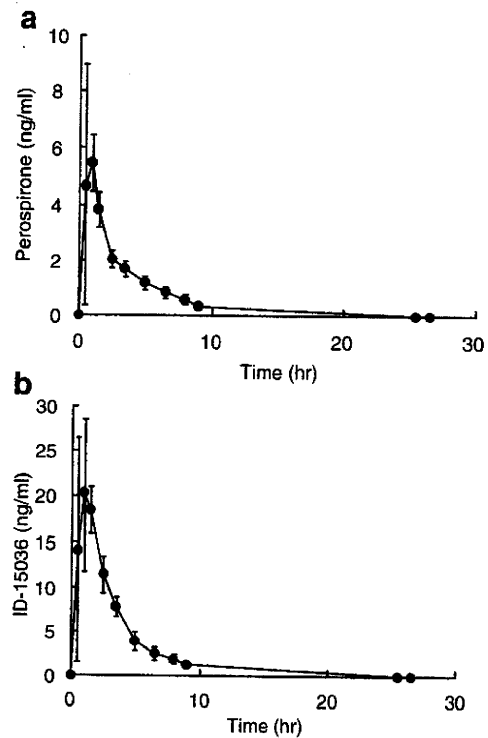

Fig. 3 Time course of mean plasma concentrations of perospirone (a) and ID-15036 (b) in healthy subjects study. *Bars* represent standard deviation of mean

benzodiazepines or anti-Parkinson drugs, and plasma prolactin levels were not measured.

Pharmacokinetics and contributions to receptor occupancy of perospirone and ID-15036

In healthy subjects, plasma concentrations of perospirone and ID-15036 peaked at 1 h after administration, with the half-lives of plasma concentrations being 2.2 and 1.9 h, respectively. The plasma concentration of ID-15036 was fourfold that of perospirone. These results were in good agreement with the previous study showing that the T_{max} values were 0.8 (perospirone) and 1.1 h (ID-15036), and $T_{1/2}$ was 1.9 h (perospirone; Yasui-Furukori et al. 2004). As ID-15036 has affinity for the dopamine D_2 receptor ($K_i =$ 5.84 nM) and blocks the dopamine D_2 receptor of the in vivo rat brain (Takahashi et al. 1998), both perospirone and ID-15036 contributed to dopamine D_2 receptor occupancy, and the plasma concentrations of both were fitted to the occupancy curve.

Effects of affinity and pharmacokinetics of antipsychotics on time course of receptor occupancy

Dopamine D_2 receptor occupancy was about 75% at 1.5 h after perospirone administration and then showed a rela-

Fig. 2 Time course of mean dopamine D_2 receptor occupancy in healthy subject study. *Bars* represent standard deviation of mean

tively rapid decline. After 25.5 h, about 30% occupancy remained, although plasma concentrations of perospirone and ID-15036 were not detectable. The time to reach half of the peak occupancy of 75% was 22 h. The time courses of receptor occupancy and plasma concentration were quite different. In comparison, risperidone and olanzapine showed sustained occupancy; about 80% occupancy 5 or 6 h after administration decreased to only 70% after 24 h (Takano et al. 2004; Tauscher et al. 2002). On the other hand, quetiapine showed transient occupancy; 64% occupancy after 2 h decreased to 0% after 24 h (Kapur et al. 2000b). Some factors such as the time course of plasma concentration of antipsychotics or affinity for dopamine D_2 receptor were considered to affect the time course of receptor occupancy (Kapur and Seeman 2001; Takano et al. 2004). For example, high affinity and long half-life of plasma concentration (e.g., risperidone (K_i=1.1 nM, $T_{1/2}$= 17.8 h) and olanzapine (K_i=5.1 nM, $T_{1/2}$=19.5 h)) expressed sustained occupancy, and low affinity and short half-life of plasma concentration (e.g., quetiapine (K_i= 122 nM, $T_{1/2}$=3.2 h)) expressed transient occupancy (Gefvert et al. 1998; Seeman 2002; Takano et al. 2004; Tauscher et al. 2002). Perospirone has high affinity for dopamine D_2 receptor and a short half-life of plasma concentration (Takahashi et al. 1998; Yasui-Furukori et al. 2004). These features may cause relatively rapid decrease in occupancy, from 75% at 1.5 h of perospirone administration to 32% after 25.5 h, but the occupancy did not completely disappear within a day. In patients taking 32 mg perospirone (number 6), dopamine D_2 receptor occupancy was 65% at 17.5 h after, supporting an intermediate time course between sustained and transient occupancy.

Possibility of new dosing schedule with perospirone

There are several opinions concerning the dosing schedule of antipsychotics. A recent clinical study reported that extended antipsychotic dosing (every second or third day) was effective and decreased side effects for chronic patients with schizophrenia (Remington et al. 2005). An animal study reported that transient antipsychotic medication was more effective for amphetamine-induced behavioral abnormality than continuous one (Samaha et al. 2008). These findings indicate that sustained occupancy might not necessarily be required for antipsychotic therapy of schizophrenia. In prodromal episode-based intervention, antipsychotic drugs were used occasionally, and long antipsychotic-free periods were sometimes inserted. However, some studies reported that intermittent medication increased the relapse rate in schizophrenia (Gaebel et al. 2002; Herz et al. 1991; Schooler et al. 1997). Because perospirone shows an intermediate time course between sustained and transient occupancy, its single administration may become a new dosing schedule choice

for an antipsychotic drug. Indeed, the administration of perospirone once a day indicated antipsychotic effects and preventions from relapse for chronic patients with schizophrenia (Kusumi et al. 2008). Four patients in the present study (numbers 1, 4, 5, and 6) taking 16 mg or more at least once a day were maintained for more than 6 months. Further study of relationships between clinical response and receptor occupancy of various dosing schedules in patients with schizophrenia will be needed.

Regional difference of dopamine D_2 receptor occupancy

Regional differences of dopamine D_2 receptor occupancy between the striatum and extrastriatum in some second-generation antipsychotic drugs have been discussed (Arakawa et al. 2008; Ito et al. 2009; Pilowsky et al. 1997; Talvik et al. 2001). In the present study, the mean occupancy of four healthy subject and two patients (number 1 and 5) in a short interval between the administration of 16 mg of perospirone and PET scanning seemed to differ very little (75.1% in the striatum with [^{11}C]raclopride and 77.0% in the temporal cortex with [^{11}C]FLB 457). It is suggested that there were no regional differences of dopamine D_2 receptor occupancy between the striatum and extrastriatum with perospirone despite the subjects, study protocols, and radioligands being different.

Conclusion

Sixteen milligrams of perospirone caused over 70% dopamine D_2 receptor occupancy near its peak level, then becoming about half after 22 h. The time courses of receptor occupancy and plasma concentration were quite different. This single dosage may be sufficient for the treatment of schizophrenia and might be useful as a new dosing schedule choice.

References

Arakawa R, Ito H, Takano A, Takahashi H, Morimoto T, Sassa T, Ohta K, Kato M, Okubo Y, Suhara T (2008) Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine D2 receptor occupancy in patients with schizophrenia. Psychopharmacology (Berl) 197:229–235

Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G (1992) Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry 49:538–544

Gaebel W, Janner M, Frommann N, Pietzcker A, Kopcke W, Linden M, Muller P, Muller-Spahn F, Tegeler J (2002) First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. Schizophr Res 53:145–159

Gefvert O, Bergstrom M, Langstrom B, Lundberg T, Lindstrom L, Yates R (1998) Time course of central nervous dopamine-D2 and 5-HT2 receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia. Psychopharmacology (Berl) 135:119–126

Herz MI, Glazer WM, Mostert MA, Sheard MA, Szymanski HV, Hafez H, Mirza M, Vana J (1991) Intermittent vs maintenance medication in schizophrenia. Two-year results. Arch Gen Psychiatry 48:333–339

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539

Ito H, Arakawa R, Takahashi H, Takano H, Okumura M, Otsuka T, Ikoma Y, Shidahara M, Suhara T (2009) No regional difference in dopamine D2 receptor occupancy by the second-generation antipsychotic drug risperidone in humans: a positron emission tomography study. Int J Neuropsychopharmacol 12:667–675

Kapur S, Seeman P (2001) Does fast dissociation from the dopamine d2 receptor explain the action of atypical antipsychotics? A new hypothesis. Am J Psychiatry 158:360–369

Kapur S, Zipursky R, Jones C, Remington G, Houle S (2000a) Relationship between dopamine D2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 157:514–520

Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P (2000b) A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. Arch Gen Psychiatry 57:553–559

Kusumi I, Masui T, Koyama T (2008) Long-term perospirone treatment with a single dose at bedtime in schizophrenia: relevant to intermittent dopamine D2 receptor antagonism. Prog Neuropsychopharmacol Biol Psychiatry 32:520–522

Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. Neuroimage 4:153–158

Nordstrom AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, Uppfeldt G (1993) Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatry 33:227–235

Onrust SV, McClellan K (2001) Perospirone. CNS Drugs 15:329–337, discussion 338

Pilowsky LS, Mulligan RS, Acton PD, Ell PJ, Costa DC, Kerwin RW (1997) Limbic selectivity of clozapine. Lancet 350:490–491

Remington G, Seeman P, Shammi C, Mann S, Kapur S (2005) "Extended" antipsychotic dosing: rationale and pilot data. J Clin Psychopharmacol 25:611–613

Samaha AN, Reckless GE, Seeman P, Diwan M, Nobrega JN, Kapur S (2008) Less is more: antipsychotic drug effects are greater with transient rather than continuous delivery. Biol Psychiatry 64:145–152

Schooler NR, Keith SJ, Severe JB, Matthews SM, Bellack AS, Glick ID, Hargreaves WA, Kane JM, Ninan PT, Frances A, Jacobs M, Lieberman JA, Mance R, Simpson GM, Woerner MG (1997) Relapse and rehospitalization during maintenance treatment of schizophrenia. The effects of dose reduction and family treatment. Arch Gen Psychiatry 54:453–463

Seeman P (2002) Atypical antipsychotics: mechanism of action. Can J Psychiatry 47:27–38

Sekine Y, Ouchi Y, Takei N, Yoshikawa E, Okada H, Minabe Y, Nakamura K, Suzuki K, Iwata Y, Tsuchiya KJ, Sugihara G, Mori N (2006) Perospirone is a new generation antipsychotic: evidence from a positron emission tomography study of serotonin 2 and D2 receptor occupancy in the living human brain. J Clin Psychopharmacol 26:531–533

Suhara T, Sudo Y, Okauchi T, Maeda J, Kawabe K, Suzuki K, Okubo Y, Nakashima Y, Ito H, Tanada S, Halldin C, Farde L (1999) Extrastriatal dopamine D2 receptor density and affinity in the human brain measured by 3D PET. Int J Neuropsychopharmacol 2:73–82

Takahashi Y, Kusumi I, Ishikane T, Koyama T (1998) In vivo occupation of dopamine D1, D2 and serotonin2A receptors by novel antipsychotic drug, SM-9018 and its metabolite, in rat brain. J Neural Transm 105:181–191

Takano A, Suhara T, Ikoma Y, Yasuno F, Maeda J, Ichimiya T, Sudo Y, Inoue M, Okubo Y (2004) Estimation of the time-course of dopamine D2 receptor occupancy in living human brain from plasma pharmacokinetics of antipsychotics. Int J Neuropsychopharmacol 7:19–26

Talvik M, Nordstrom AL, Nyberg S, Olsson H, Halldin C, Farde L (2001) No support for regional selectivity in clozapine-treated patients: a PET study with [11C]raclopride and [11C]FLB 457. Am J Psychiatry 158:926–930

Tauscher J, Jones C, Remington G, Zipursky RB, Kapur S (2002) Significant dissociation of brain and plasma kinetics with antipsychotics. Mol Psychiatry 7:317–321

Yasui-Furukori N, Inoue Y, Tateishi T (2003) Determination of a new atypical antipsychotic agent perospirone and its metabolite in human plasma by automated column-switching high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 789:239–245

Yasui-Furukori N, Furukori H, Nakagami T, Saito M, Inoue Y, Kaneko S, Tateishi T (2004) Steady-state pharmacokinetics of a new antipsychotic agent perospirone and its active metabolite, and its relationship with prolactin response. Ther Drug Monit 26:361–365

教 育 講 演

カタトニア（緊張病）症候群の診断と治療

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1. は じ め に

カタトニア (catatonia，緊張病) は，ICD-10 や DSM-IV では，主に緊張型として統合失調症の一亜型として診断されている．しかしながら，カタトニアは，統合失調症だけではなく気分障害や器質性精神障害においても認められることがあり，加えて原疾患の如何にかかわらず一定の治療法が有効なことから，カタトニアを呈する状態を一つの症候群として扱い，治療を行うことが推奨されている[2,9]．

2. カタトニア概念の歴史的変遷

カタトニアは，Kahlbaum のカタトニアにその概念の起源をもつ．Kahlbaum の考えたカタトニアはメランコリー，マニー，昏迷，錯乱，最終的には精神荒廃という一連の病像を呈し，精神症状とともに，けいれん，強硬，蠟屈，音唱などの運動症状を呈する循環性に変遷する経過をたどる大脳疾患であった．Kahlbaum のカタトニアは精神荒廃に至るものだけではなく，循環性の経過をとりながら寛解に至る予後良好なものを含んでいた．しかしながら，Kraepelin はカタトニアを循環性の経過や病相の変遷をとる単一精神病と考えなかった．けいれんや緊張など運動症状より，随意運動の障害という点から症状をとらえ，必ずしも予後不良でない弛緩性アトニアやカタトニア性躁病を除外し，慢性に経過して荒廃に至る慢性カタトニアに注目して，破瓜病と同じ早発性痴呆の一亜型として規定した．その Kraepelin の考え方が現代の診断概念にも引き継がれ，DSM や ICD において，カタトニアは主に統合失調症の一亜型として診断されてきた．

Kraepelin の早発性痴呆概念とは別に，Wernicke は，過動，寡動，無動など運動症状が周期性，持続性，混合性に現れ精神運動症状を主症状とする精神病を運動精神病として抽出した．この概念を引き継いだ Wernicke-Kleist-Leonhard 学派では，精神運動症状を主症状とする精神病を，感情，妄想，幻覚の多形性症状を呈する多動と無動が双極性に経過し寛解する類循環精神病，急性発症で多動と無動の双極性の経過をとりながら，完全寛解せず残遺状態に至る周期性カタトニア，潜行性の発症で慢性進行性の経過をとり寛解に至らず不可逆性の残遺状態に至る系統カタトニアに分類した[6]．周期性カタトニアを系統カタトニアから区別するか否かについて近年精力的な研究が行われてきた．その結果によると，同診断法の診断者間信頼性は高く，5年間以上にわたり他の診断に変わることなく安定しており，生物学的にも周期性カタトニアでは系統カタトニアよりも冬生まれが少なく，逆に遺伝負因がより強いことから，系統カタトニアから周期性カタトニアを分ける妥当性が示されたという．さらに，周期性カタトニアの遺伝研究では，家族集積，双生児で一致率が高いことが報告されるとともに，連鎖研究で 15q15 と 22q13 との連鎖が報告されている．

Kraepelin, そして Wernicke - Kleist - Leonhard 学派の考え方はカタトニアに一定の病因, 病態, 症候, 経過を示す疾病単位を求めようとする考え方であったが, このような疾病単位を目指す考え方, とくに統合失調症の一亜型という考え方に見直しをせまる契機になったのは Gelenberg の報告[3] であった.

Gelenberg は, カタトニアが統合失調症だけではなく, 気分障害や神経症などの精神疾患, 神経疾患, 代謝疾患, 中毒疾患などさまざまな身体疾患でも出現することから, カタトニアを自動的に統合失調症の一亜型と考えることに注意を喚起した. そして, カタトニアは, さまざまな原因によってひき起こされる症候群であり, カタトニア症候群をきたす身体疾患についても留意すべきと推奨した. このような考えは, カタトニアに疾患単位を求めるのではなく, 一定の症候を呈する症候群として扱おうとする考えで, カテゴリーモデルによる診断から, ディメンジョンモデルによる診断への転回である.

実際に, 疫学調査[1] によると, カタトニアは, 統合失調症では報告による違いが大きいものの概ね5％以下の割合であるのに対して, 気分障害では13〜31％に認められ, 特に双極性障害に関連して認められることがより多いという. またカタトニアを呈した症例を検討すると原疾患は統合失調症や気分障害だけに限らず, 約4分の1は器質性精神障害においても認められたという. 以上の疫学データからもカタトニア症状のみでは原疾患を特定することは困難であることは明らかである. さらに, カタトニアはしばしば身体合併症を伴うことが多く, 発熱や自律神経失調を合併した悪性カタトニア[4] ではさらに重篤な身体合併症の危険性が高く, 治療の遅れは致死的な転帰をもたらすことがある. 加えて, カタトニアは原疾患の如何にかかわらず, 後述するような一定の治療法が有効なことから, カタトニアを呈する状態を一つの症候群として診断し, 早急な治療にあたることが推奨される.

3. カタトニア症候群の診断

DSM-Ⅳ-TR では, カタトニア型統合失調症の症状として, 1）カタレプシーまたは昏迷として示される無動症, 2）興奮（過度で無目的の運動）, 3）極度の拒絶症あるいは無言症, 4）姿勢保持, 常同運動, しかめ面などの特徴的な自発運動の奇妙さ, 5）反響言語または反響動作をあげ, 以上のうち少なくとも2つが優勢である統合失調症を緊張型と診断している. このような DSM の診断基準については, カタレプシー, 拒絶症, 無言症, 反響症状といったカタトニアに特異的な症状と, 過度の運動活動や重症の無動などの非特異的症状を同列に扱っている. 1）, 3）, 5）項はすべて姿勢性無動であり内容に重複が認められる. 反響症状など一過性にしか認められない症状があるにもかかわらず症状の持続期間が定義されていないなどの問題点が指摘されており, Fink と Taylar によって特異的症状に重みをつけて, 症状の持続時間を明示した診断基準[2] が提案されている. 同診断基準では, A. 無動, 無言, 昏迷が少なくとも1時間持続し, カタレプシー, 命令自働, 姿勢常同（2回以上観察または誘発されること）を少なくとも1つ以上伴うか, B. 無動, 無言, 昏迷がない場合は常同症, 反響現象, カタレプシー, 命令自働, 姿勢常同, 拒絶性, 両価性いずれかの症状を少なくとも2つ以上, 2回以上観察または誘発されることとなっている.

カタトニアの経過で, 発熱や自律神経失調を呈する場合は予後不良な場合があり, かっては致死性カタトニアと呼ばれた. しかしながら, 適切な治療と身体管理によって救命できることから, 最近は悪性カタトニアと診断される. 抗精神病薬による悪性症候群は, ドーパミン遮断によって悪性カタトニアが誘発されたものであるという考え方が提案されており, 両者には類縁の病態が考えられている. カタトニア症候群の治療において, 悪性カタトニアへの移行を常にモニターしながら治療にあたる必要がある.

4．カタトニア症候群の薬物療法

カタトニアを統合失調症の一亜型としてとらえる考え方からは，統合失調症の治療に準じて抗精神病薬の投与が推奨されることになる．カタトニアの場合は，しばしば興奮が激しく，拒絶を認めることからハロペリドールなどの力価の強い抗精神病薬の経口または経静脈投与が試みられる場合が多かった．しかしながら，カタトニアをさまざまな精神疾患，身体疾患で認められる症候群と考えると，悪性症候群あるいは悪性カタトニアのリスクを高める抗精神病薬は推奨できず，ベンゾジアゼピンがカタトニア治療の第一選択薬として推奨される．

カタトニア症候群の急性エピソードに対して，ロラゼパム1〜2mgの効果を調べたオープン試験[8]では，12回（80％）で2時間以内に急速に症状の消失が認められた．著効を認めた中には，気分障害や統合失調症だけではなく，器質性精神障害としてのカタトニア症候群も含まれていたことから，原因疾患にかかわらず，カタトニア症候群に対するロラゼパムの有用性が確かめられた．この他にも，急性カタトニア症候群に対して低用量のロラゼパムは，70〜90％[8,11,12]の良好な改善率を示すことが確かめられている．

カタトニア症候群の原因疾患とロラゼパムの効果の関連については，さまざまな精神疾患や身体疾患で80％を越える例でロラゼパムが著効を示すのに対して，統合失調症のカタトニアに対してはロラゼパムの効果が20〜30％にとどまるという報告もある．これまでロラゼパムのカタトニアに対する有効性を二重盲検試験で調べた唯一の報告[10]によると，慢性統合失調症患者の慢性カタトニアに対して，ロラゼパムの有効性は検証されなかった．このような統合失調症の症例においては抗精神病薬の併用療法が行われるが，主治医は悪性症候群を惹起するジレンマに悩まされることになる．少なくとも高力価の定型抗精神病薬の大量療法は避けるべきである．

5．カタトニアの電気けいれん療法（ECT）

1934年，Medunaは樟脳油（camphor）を注射することによってけいれんを誘発し，早発性痴呆患者を治療することに成功した．Medunaの症例は4年間にわたり昏迷状態を呈した患者であった．続く1938年，CerlettiとBiniはけいれんを誘発する方法を電流に変えて精神病患者の治療を行い電気けいれん療法（ECT）への道を開いた．この時の症例は興奮と昏迷を交代した患者であった．このようにECT開発の端緒となった歴史的な症例はカタトニア症候群を呈していたと思われる．そのカタトニア症状にけいれん療法が劇的な効果をもたらしたことは，現在のカタトニア症候群の治療におけるECTの重要性を考えると興味深い．

カタトニア症候群に対するECTの効果に関するコントロール試験は報告されていない．しかしながら，カタトニアに対するECTの効果を調べたオープン試験あるいは症例報告では，70％から100％の症例で効果が得られるという良好な結果が報告されている[2,5]．その成績は，しばしばベンゾジアゼピンの効果よりも優れ，特に，生命の危険がある悪性カタトニアに対してはベンゾジアゼピン治療よりもECTで，より良好な成績が報告されている．ECTのカタトニアに対する有効性は確立しているものの，より簡便で侵襲の少ない低用量でのベンゾジアゼピン治療に高い有効性が確認されていることから，第一に選択すべき治療としてベンゾジアゼピンの投与が推奨される．ベンゾジアゼピンが無効な場合や，生命の危険がある悪性カタトニアの場合にはECTの適応になる[1]．

ECTの治療効果とカタトニア症候群の原因疾患の関連について調べた報告は多くないが，統合失調症におけるカタトニア症候群の寛解率71％に対して，気分障害における寛解率は96％とより高かったという[7]．さらに，ECTの治療反応性を予測する症状としては，原因疾患がうつ病の場合は精神運動抑制が指摘されている．

ECTの方法については，カタトニア症候群に
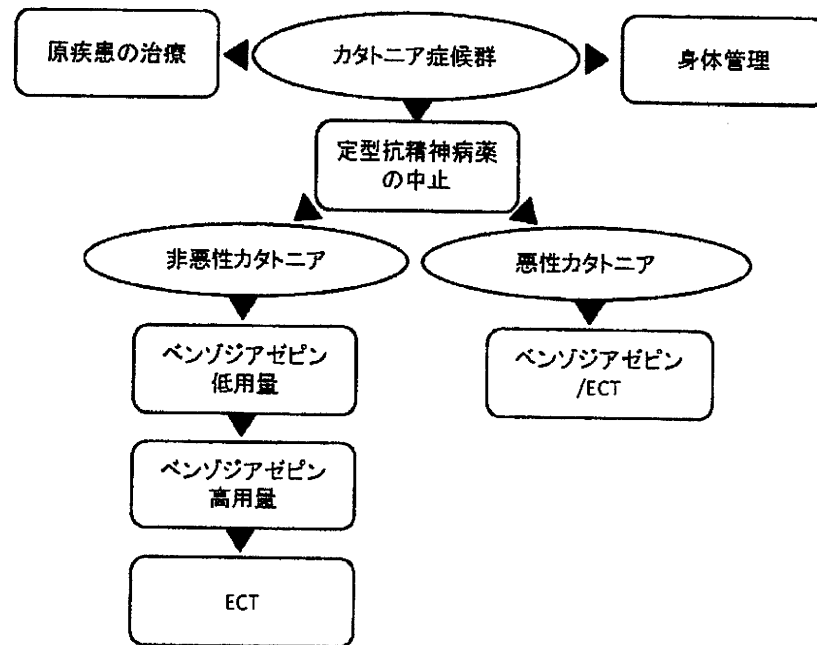
図 カタトニア症候群の治療アルゴリズム[5]

対する特異的な方法が推奨されているわけではない．両側側頭電極配置で短パルス電流を年齢の半分の電気量から開始する方法が推奨されている．カタトニア症候群の場合，第一選択薬であるベンゾジアゼピンが先に投与されているため，けいれん閾値が上がり有効なけいれんが得られない場合がある．その場合は，ベンゾジアゼピン拮抗薬フルマゼニルをECT直前に投与することによって有効なけいれんが得られる[2]．ベンゾジアゼピンが効果不十分の場合に，ECTを行うためにベンゾジアゼピンを中止する方法が一般的であったが，フルマゼニルを使用することによって，ベンゾジアゼピンを継続しながらECTを併用するベンゾジアゼピンとECTの併用療法が可能になる．

6. カタトニア症候群の治療アルゴリズム

欧米の治療アルゴリズムを参考に作成した当教室におけるカタトニア症候群の治療アルゴリズム[5]について紹介する（図）．

カタトニア症候群はさまざまな精神疾患や身体疾患にみられる一定の症候群であるから，診断は症候の観察に基づくFinkとTaylarの診断基準

に基づいて行う．実際の治療にあたっては，まず全身の身体管理，原疾患の鑑別診断，治療が重要である．カタトニア症候群では，しばしば経口摂取が困難になっていることから，一般的な輸液などの身体管理が必要となる．さらに，カタトニア症候群に伴っておこる身体合併症は，咽頭筋障害による誤嚥性肺炎，無気肺，長期臥床による褥瘡，深部静脈血栓症，肺血栓塞栓症，経口摂取不能による低栄養，脱水，圧迫による絞扼性の神経障害，筋固縮，尿路感染症など多岐にわたり，これらの身体合併症の注意深い管理治療が必要である．とくに悪性カタトニアの場合は，高熱による脱水，自律神経症状による心負荷の影響などがあり，身体管理を注意深く行う必要がある．

カタトニア症候群はさまざまな身体疾患を原因疾患として起こりうるが，身体疾患に伴うカタトニア症候群の場合は，身体疾患に対する治療が必要で著効を示すことがある．たとえば，非けいれん性のてんかん発作重積状態に対する抗てんかん薬の投与などである．

カタトニア症候群を統合失調症の一亜型とみる考え方から，以前はカタトニア症候群に対して高

力価の定型抗精神病薬ハロペリドールを経口また
は非経口的に投与する治療法が一般的であった.
しかしながら，高力価の定型抗精神病薬は悪性カ
タトニアを惹起するリスクが高いため使用すべき
ではなく，投与されていた場合は中止すべきであ
る.

　カタトニア症候群の原因疾患が統合失調症や気
分障害の場合，原因疾患の治療としての非定型抗
精神病薬は有効とする報告もあることから，臨床
症状を注意深く観察しながら投与を試みてもよい.
ただし，非定型抗精神病薬の中にもドーパミン
D2 受容体遮断作用の強い高力価格のものから低
力価のものまである，また定型抗精神病薬の中に
も低力価のものがあり，どのような抗精神病薬の
投与が勧められるかについてはさらなる検討が必
要である．ただし，すくなくとも悪性カタトニア
の場合は抗精神病薬を使用すべきではない.

　カタトニア症候群に自律神経系の不安定と高熱
が合併した場合に悪性カタトニアを考えなくては
いけない．そのような症状がない非悪性のカタト
ニア症候群の場合には，ベンゾジアゼピン低用量
から開始し，無効であれば増量し，数日で改善が
認められない場合は ECT を導入する.

　一方，悪性カタトニアの場合には，身体的な重
症度にもよるが，治療が遷延することで合併症の
可能性が高まることから，ベンゾジアゼピン高用
量の投与と同時に ECT の開始を考慮すべきであ
る．ベンゾジアゼピンの抗けいれん作用により
ECT 効果の減弱が予想されるが，ベンゾジアゼ
ピンの投与スケジュールの調節や，麻酔前にベン
ゾジアゼピン拮抗薬を併用することによって十分
な ECT 効果が達成できる.

7. 結　語

　カタトニア症状は統合失調症の一亜型としてよ
りも気分障害において認められることが多い．ま
た，器質性精神障害においても認められることが
あり，発熱や自律神経失調を合併した悪性カタト
ニアではさらに重篤な身体合併症の危険性が高く，
治療の遅れは致死的な転帰をもたらすことがある.

加えて，カタトニア症状は原疾患の如何にかかわ
らず，ベンゾジアゼピンなどの薬剤と ECT が有
効なことから，カタトニア症状を呈する状態を一
つの症候群として扱い，早急な治療を行うことが
推奨される．高力価定型抗精神病薬は高熱と自律
神経症状を合併した悪性カタトニアを惹起する危
険性から投与すべきではない．非定型抗精神病薬
は悪性カタトニアでないカタトニア症状に対して，
統合失調症や気分障害などの原疾患の治療として
有効なことがある.

文　献

1) Caroff, S.N., Mann, S.G., Francis, A., et al.: Catatonia. From psychopathology to neurobiology. American Psychiatric Publishing, Washington DC, 2004

2) Fink, M., Taylor, M.A.: Catatonia: A clinicians' guide to diagnosis and treatment. Cambridge University Press, Cambridge, 2003 (鈴木一正訳: カタトニア．臨床医のための診断・治療ガイドライン．星和書店，東京，2007)

3) Gelenberg, A.J.: The catatonic syndrome. Lancet, 1; 1339-1341, 1976

4) Hafner, H., Kasper, S.: Acute life-threatening catatonia. Nervenarzt, 53; 385-394, 1982

5) 端山央理，斉藤卓弥，大久保善朗: 今日の精神科治療指針 2006．精神科における症候・症候群の治療指針 緊張病症状．臨床精神医学，35; 254-259, 2006

6) Pfuhlmann, B., Stober, G.: The different conceptions of catatonia: historical overview and critical discussion. Eur Arch Psychiatry Clin Neurosci, 251 (Suppl. 1); 4-7, 2001

7) Rohland, B.M., Carroll, B.T., Jacoby, R.G.: ECT in the treatment of the catatonic syndrome. J Affect Disord, 29; 255-261, 1993

8) Rosebush, P.I., Hildebrand, A.M., Furlong, B. G., et al.: Catatonic syndrome in a general psychiatric inpatient population: frequency, clinical presentation, and response to lorazepam. J Clin Psychiatry, 51; 357-362, 1990

9) Taylor, M.A., Fink, M.: Catatonia in psychiatric classification: a home of its own. Am J Psychiatry, 160; 1233-1241, 2003

10) Ungvari, G.S., Chiu, H.F., Chow, L.Y., et al.:

Lorazepam for chronic catatonia : a randomized, double-blind, placebo-controlled cross-over study. Psychopharmacology (Berl) 142 ; 393-398, 1999

11) Ungvari, G.S, Leung, C.M., Wong M.K., et al. : Benzodiazepines in the treatment of catatonic syndrome. Acta Psychiatr Scand, 89 ; 285-288, 1994

12) Yassa, R., Iskandar, H., Lalinec, M., et al. : Lorazepam as an adjunct in the treatment of catatonic states : an open clinical trial. J Clin Psychopharmacol, 10 ; 66-68, 1990

Short Communication

Chronic repetitive transcranial magnetic stimulation failed to change dopamine synthesis rate: Preliminary L-[β-11C]DOPA positron emission tomography study in patients with depression

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We have examined the effects of repetitive transcranial magnetic stimulation (rTMS) on central dopaminergic function in patients with depression using positron emission tomography with L-[β-11C]DOPA, a ligand to assess the rate of endogenous dopamine synthesis. Eight patients were treated with 10-daily sessions of rTMS over the left dorsolateral prefrontal cortex. Positron emission tomography scanning was performed in each patient twice, before the first session and 1 day after the last session. Although four out of eight patients responded to rTMS, there were no changes in the striatal dopamine synthesis rate (k) following rTMS. These results suggest that chronic rTMS had a limited effect on the dopaminergic system.

Key words: depression, dopamine synthesis, L-[β-11C]DOPA, positron emission tomography, repetitive transcranial magnetic stimulation.

TRANSCRANIAL MAGNETIC STIMULATION is a non-invasive method of brain stimulation in which magnetic fields are used to induce electric currents in the cerebral cortex, depolarizing neurons. Though it has been reported that repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) is an effective treatment for depression,[1,2] its precise mechanisms are poorly understood. However, the involvement of the dopaminergic system has been suggested in elucidating the therapeutic mechanisms of rTMS. Several

human studies demonstrated that acute rTMS induced the release of endogenous dopamine in the striatum.[3–5] Nevertheless, we recently reported that there were no changes in [11C]raclopride binding in the striatum after 10-daily rTMS treatment in the patients with depression.[6] In the present study, we have examined the effects of 10-daily sessions of rTMS on dopaminergic function in depressed patients using positron emission tomography (PET) with L-[β-11C]DOPA. L-[β-11C]DOPA can be used to assess the rate of endogenous dopamine synthesis as a way to estimate presynaptic function of the central dopaminergic system.[7]

METHOD

Eight patients (four women and four men aged 36.8 ± 6.4 years [mean $\pm$ SD]) with a DSM-IV-TR diagnosis of major depressive disorder participated in

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this study. Three patients had a recurrent type of depressive disorder (one patient had two previous episodes and two patients had one previous episode). Duration of the present episodes was 20.5 ± 13.3 months. They were all right-handed. The patients were free of somatic or neurological disorders on the basis of their medical history, blood test, electrocardiogram, chest X-rays, brain computed tomography and electroencephalogram. Their clinical pictures were melancholic without psychotic or catatonic features. Their suicide ideas were not strong. They had no comorbid psychiatric disorders, such as anxiety disorders, alcohol dependence or personality disorders. The patients were resistant to or intolerant of drug treatment. One patient did not respond to electroconvulsive therapy. Three patients were resistant to two adequate trials of antidepressants. Two patients did not respond to one adequate antidepressant trial. Three patients had taken atypical antipsychotics as augmentation agents. They had at least a 4-week washout period from their previous medication. Fluvoxamine and lorazepam were allowed during the washout period with little clinical improvement and pharmacological dosages were kept constant during the study. The average dose of fluvoxamine during the study was 115.6 ± 88.6 mg/day. Six patients had not been able to take fluvoxamine in sufficient dosage, more than 150 mg/day, because of side-effects, such as sleepiness, anxiety, and nausea. This study was approved by the human ethics committees of Tokyo Medical and Dental University, Tokyo, Japan, and the National Institute of Radiological Sciences, Chiba, Japan. Following a description of all procedures, subjects provided written informed consent.

The Magstim Rapid System (Magstim Company Limited, Spring Gardens, Whitland, UK) with an eight-shaped coil was used to administer the rTMS treatments. Each patient was treated with 10 sessions (five times per week for 2 weeks) using the following parameters per session: 10 Hz frequency, 20 trains of 5 s duration separated by 25 s, and an intensity of 100% motor threshold (MT). These parameters were within the safety criteria.[8] At entry, each patient's MT was determined using the visual method with the right first dorsal interosseous (FDI) muscle as the target muscle.[9] MT was defined as the stimulus intensity that produced visibly observable right FDI muscle contractions at least five times out of 10 stimuli. rTMS was performed over the left dorsolateral prefrontal cortex (DLPFC). The point of left

DLPFC was determined by moving the coil 5 cm anteriorly from the point of MT determination. The point of stimulation was marked for reference with an indelible skin marker. MT and coil placement were rechecked after the fifth treatment to assess, but neither MT nor coil placement was readjusted for any patient. During rTMS the patients wore earplugs to dampen the loud noise from the discharging coil.

To assess improvement of the clinical symptoms, all patients were evaluated with the 17-item Hamilton Rating Scale for Depression (HRSD)[10] twice: 1 day before and 1 day after a series of rTMS.

The first study was performed before a series of rTMS and the second study was performed 1 day after the last session of rTMS. Each PET scan began more than 3 h after the last medication. All PET studies were performed with an ECAT EXACT HR+ (CT1-Siemens, Knoxville, TN, USA) in 3-D mode, which provides 63 planes with a 15.5-cm axial field of view.

L-[β-^{11}C]DOPA was synthesized from [^{11}C]carbon dioxide via D,L-[3-^{11}C]alanine as described previously.[11,12] After a 10-min transmission scan with a ^{68}Ge-^{68}Ga source, a bolus of L-[β-^{11}C]DOPA was rapidly injected into the antecubital vein with a 20-ml saline flush. Injected dose was 9.9 ± 1.8 mCi and 10.2 ± 0.5 mCi before and after rTMS, respectively. The specific radioactivity was 78.3 ± 42.5 GBq/μmol and 52.3 ± 16.2 GBq/μmol before and after rTMS, respectively. Dynamic PET scanning was started immediately after the injection and continued for 60 min.[13] A head fixation device with thermoplastic attachments for individual fit minimized head movement during PET measurements. All emission scans were reconstructed using a Hanning filter with a cut-off frequency of 0.4 cycle/pixel (FWHM [full width at half maximum] = 7.5 mm).

Magnetic resonance (MR) images were obtained with a Philips Gyroscan NT, 1.5 tesla. Scan parameters were 1-mm thick 3-D T1-weighted images with a transverse plane. All MR images were coregistered to the PET images using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROI) were manually placed on coregistered MR images and transferred to the corresponding PET images. ROI were set to cover three adjacent slices for the right and left caudate nucleus, right and left putamen and occipital cortex. Then, time-activity curves were obtained. For quantification of the striatal utilization of L-[β-^{11}C]DOPA, the graphical analysis method using reference brain

Table 1. Changes in k values of L-[β-^{11}C]DOPA in the striatum

Region	k before TMS	k after TMS
R Caudate	0.01435 ± 0.00327	0.01264 ± 0.00171
L Caudate	0.01400 ± 0.00184	0.01361 ± 0.00430
R Putamen	0.01495 ± 0.00145	0.01475 ± 0.00234
L Putamen	0.01507 ± 0.00223	0.01446 ± 0.00150

Values are mean ± SD.
L, Left; R, right; TMS, transcranial magnetic stimulation.

region (occipital cortex) developed by Patlak and Blasberg[7,14] was used to calculate dopamine synthesis rate (k).

Response to treatment was defined as an HRSD less than 10 points or a 50% decrease in HRSD 1 day after rTMS. Paired t-test was used to statistically analyze the difference between HRSD scores 1 day before the first session and 1 day after the last session of rTMS. Values of $P < 0.05$ were considered significant.

Statistical analysis of the difference between k values in patients measured before rTMS and 1 day after the last session of rTMS was performed using two-way repeated ANOVA to find interaction between time (before and after) and regions (right and left caudate nucleus, right and left putamen). When we found any interaction, post-hoc Bonferroni correction was used for multiple comparisons. Values of $P < 0.05$ were considered significant.

RESULTS

All patients tolerated rTMS without severe complications. HRSD scores decreased significantly following a series of rTMS (17.0 ± 2.4 before treatment; 10.6 ± 6.4 after treatment; $P = 0.005$, paired t-test). Four out of eight patients responded to rTMS.

Two-way repeated ANOVA revealed no significant interactions between time and regions with regard to k-values for L-[β-^{11}C]DOPA [F (3, 5) = 0.382, $P = 0.771$] (Table 1).

DISCUSSION

This study has demonstrated that k-values of L-[β-^{11}C]DOPA did not change in the striatum following rTMS. These results suggest that the rate of dopamine synthesis in the striatum did not significantly change 1 day after the last session of rTMS.

In our previous study, rTMS induced no significant changes in [^{11}C]raclopride binding in the striatum.[6] The results were not consistent with previous reports,[3–5] showing that rTMS caused a reduction in [^{11}C]raclopride or [^{123}I]IBZM binding, indicating increased release of endogenous dopamine. This discrepancy could be explained by the following two reasons: first, we started [^{11}C]raclopride PET scans about 24 h after the last session of rTMS, whereas the other authors started them soon after the rTMS session. Second, we applied chronic rTMS (multiple treatments), whereas the other authors used acute rTMS (single treatment). Therefore, we suggest that release of striatal dopamine induced by rTMS might only be transient, or that dopamine release may be attenuated following chronic rTMS. Tsukada et al.[15] reported that dopamine synthesis rate, as measured by L-[β-^{11}C]DOPA, could be more sensitive to evaluate the changes in dopaminergic neuronal activity than the ligand-receptor binding. Thus, present PET studies using L-[β-^{11}C]DOPA also indicated that chronic rTMS had limited effect on the dopaminergic system.[6]

A major limitation of this study is the small sample size. Another shortcoming was the study design of an open trial lacking a sham-treated rTMS group. Placebo clinical effects could not be excluded. The drugs might have influenced dopamine synthesis as three patients had taken atypical antipsychotics and all of the patients had been previously treated with antidepressants. Because treatment duration and stimulation intensity in this study were insufficient by today's standards,[1] further larger sample sizes and sham-controlled studies with longer duration and higher intensity on drug-free patients are needed.

In conclusion, although rTMS showed some efficacy for the treatment of depression, rTMS failed to change the striatal dopamine synthesis rate, as measured by L-[β-^{11}C]DOPA PET. These results suggest that chronic rTMS had limited effect on the dopaminergic system.

ACKNOWLEDGMENT

REFERENCES

1. Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. *Can. J. Psychiatry* 2008; 53: 555–566.
2. Schutter DJLG. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol. Med.* 2009; 39: 65–75.
3. Stafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J. Neurosci.* 2001; 15: RC157.
4. Stafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain* 2003; 126: 2609–2615.
5. Pogarell O, Koch W, Popperl G *et al.* Striatal magnetic stimulation in major depression: preliminary results of a dynamic [123I]IBZM SPECT study. *J. Psychiatr. Res.* 2006; 40: 307–314.
6. Kuroda Y, Motohashi N, Ito H *et al.* Effects of repetitive transcranial magnetic stimulation on [¹¹C]raclopride binding and cognitive function in patients with depression. *J. Affect. Disord.* 2006; 95: 35–42.
7. Ito H, Ota M, Ikoma Y *et al.* Quantitative analysis of dopamine synthesis in human brain using positron emission tomography with L-[β-¹¹C]DOPA. *Nucl. Med. Commun.* 2006; 27: 723–731.
8. Wassermann EM. Risk and safety repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. *Electroencephalogr. Clin. Neurophysiol.* 1998; 108: 1–16.
9. Wassermann EM, Wang B, Zeffiro TA *et al.* Locating the motor cortex on the MRI with transcranial magnetic stimulation and PET. *Neuroimage* 1996; 3: 1–9.
10. Hamilton N. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 1960; 23: 56–62.
11. Bjurling P, Watanabe Y, Oka S, Nagasawa T, Yamada H, Langstorm B. Multi-enzymatic syntheses of beta-¹¹C-labeled L-tyrosine and L-DOPA. *Acta Chem. Scand.* 1990; 44: 183–188.
12. Sasaki M, Ikemoto M, Mutoh M *et al.* Automatic synthesis of L-[β-¹¹C]amino acids using an immobilized enzyme column. *Appl. Radiat. Isot.* 2000; 52: 199–204.
13. Gefvert O, Lindstorm LH, Waters N, Waters S, Carlsson A, Tedroff J. Different corticostriatal patterns of L-DOPA utilization in patients with untreated schizophrenia and patients treated with classical antipsychotics or clozapine. *Scand. J. Psychol.* 2003; 44: 289–292.
14. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data generalization. *J. Cereb. Blood Flow Metab.* 1985; 5: 584–590.
15. Tsukada H, Miyasato K, Harada N, Nishiyama S, Fukumoto D, Kakiuchi T. Nicotine modulates dopamine synthesis rate as determined by L-[β-¹¹C]DOPA: PET studies compared with [¹¹C]raclopride binding in the conscious monkey brain. *Synapse* 2005; 57: 120–122.