Positron Emission Tomography Measurement of Dopamine D_2 Receptor Occupancy in the Pituitary and Cerebral Cortex: Relation to Antipsychotic-Induced Hyperprolactinemia

Ryosuke Arakawa, MD, PhD; Masaki Okumura, MD; Hiroshi Ito, MD, PhD; Akihiro Takano, MD, PhD; Hidehiko Takahashi, MD, PhD; Harumasa Takano, MD, PhD; Jun Maeda, PhD; Yoshiro Okubo, MD, PhD; and Tetsuya Suhara, MD, PhD

Objective: Hyperprolactinemia is a common side effect of antipsychotic drugs used in the treatment of schizophrenia. However, the magnitude of hyperprolactinemia differs among antipsychotics, and there is no reliable mechanism-related marker for the risk of hyperprolactinemia that would allow us to characterize antipsychotics.

Method: In this study, 11 healthy male subjects taking different doses of sulpiride and 24 male patients with *DSM-IV*–diagnosed schizophrenia taking different antipsychotic drugs (risperidone, olanzapine, haloperidol, and sulpiride) participated. Positron emission tomography scanning using [^{11}C] FLB 457 was performed on all subjects. The dopamine D_2 receptor occupancy of antipsychotics in the pituitary and temporal cortex was calculated. Correlations between plasma concentration of prolactin and dopamine D_2 receptor occupancies were evaluated. The ratio of drug concentration of cerebral receptor site to that of pituitary receptor site (brain/plasma concentration ratio; B/P ratio) was calculated from the receptor occupancies in the 2 regions. Data were collected between November 2001 and September 2007.

Results: Significant positive correlation was observed between the plasma concentration of prolactin and dopamine D_2 receptor occupancy in the pituitary by all 4 antipsychotics ($P = .001$). Dopamine D_2 receptor occupancies of sulpiride were markedly different between the pituitary and temporal cortex, and the B/P ratio for sulpiride (0.34) was significantly lower than for olanzapine ($P = .007$) and risperidone ($P = .015$). Olanzapine had a relatively high B/P ratio (2.70), followed by haloperidol (2.40) and risperidone (1.61).

Conclusions: Dopamine D_2 receptor occupancy in the pituitary is a good indicator of hyperprolactinemia. B/P ratio, indicating the penetrating capability across the blood-brain barrier, seems to be a good characteristic biomarker of each antipsychotic drug for the risk of hyperprolactinemia at therapeutic dose.

J Clin Psychiatry 2010;71(9):1131–1137

Submitted: *April 17, 2008; accepted April 15, 2009.*
Online ahead of print: *February 23, 2010 (doi:10.4088/JCP.08m04307yel).*
Corresponding author: *Tetsuya Suhara, MD, PhD, Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences 4-9-1, Anagawa, Inage-ku, Chiba, 263-8555, Japan (suhara@nirs.go.jp).*

Hyperprolactinemia is a commonly encountered side effect of antipsychotic drugs in the treatment of schizophrenia,[1,2] and several deficits, such as galactorrhea and sexual dysfunction, can result. For women, amenorrhea and infertility are severe adverse effects, and long-term hyperprolactinemia causes osteoporosis in relation to hypogonadism.[1,3] Hyperprolactinemia is one of the major reasons for discontinuing antipsychotic drugs,[4] but the risk for this condition varies among them.[5–8] It has been reported that antipsychotics such as risperidone and amisulpride showed a high risk, and several factors have been discussed in relation to this risk,[5–9] such as affinity for dopamine D_2 receptors[6,8] and the pharmacodynamics in plasma and brain.[9]

Prolactin secretion is controlled by tonic inhibition of dopamine on tuberoinfundibular neurons.[10,11] Hyperprolactinemia is reported to be induced by the blocking of dopamine D_2 receptors in the pituitary. As the pituitary is located outside of the blood-brain barrier, drug effects on dopamine D_2 receptors would differ between it and the brain parenchyma.[9] However, there has been no report about this relation in the living human brain.

Previous positron emission tomography (PET) studies focused on extrapyramidal side effects of antipsychotics induced by over 80% of striatal dopamine D_2 receptor occupancy.[12–14] Since dopamine D_2 receptor density in the pituitary is low ($B_{max} = 1.3$ pmol/g tissue) compared to the striatum ($B_{max} = 16.6$ pmol/g tissue),[15] measurement of dopamine D_2 receptor binding in the pituitary is difficult using a radioligand with relatively low affinity such as [^{11}C]raclopride. [^{11}C] FLB 457 has very high affinity for dopamine D_2 receptors,[16] and since it is used to measure dopamine D_2 receptors in extrastriatal regions where their density is very low,[17–21] it can also be used to measure dopamine D_2 receptor binding in the pituitary. Although some studies have reported the visualization or occupancy of human pituitary dopamine D_2 receptors,[22–24] the quantification of dopamine D_2 receptor occupancy in the pituitary by several antipsychotics using PET has not been reported.

In this study, we aimed to investigate biomarkers for the potential risk of antipsychotic drug–induced hyperprolactinemia in the living human brain. Dopamine D_2 receptor occupancies in the pituitary and temporal cortex were measured using [^{11}C]FLB 457 by different doses of sulpiride in healthy subjects to examine the dose-occupancy relationship in the 2 regions and by various antipsychotic drugs

in patients with schizophrenia to examine the relation with hyperprolactinemia.

METHOD

Subjects and Study Protocol

Study of healthy subjects receiving different doses of sulpiride. Eleven healthy male subjects (age range, 21–40 years; mean ± SD = 27.1 ± 5.8 years) participated in this study. Two PET scans using [^{11}C]FLB 457 were performed before and 3 hours after a single dose of sulpiride at 200 mg (n = 3), 400 mg (n = 3), 600 mg (n = 3), and 800 mg (n = 2). Just before the second PET scan, venous blood samples were taken to measure the plasma concentration of prolactin.

Study of patients with schizophrenia receiving different antipsychotics. Twenty-four male patients (age range, 21–49 years; mean ± SD = 37.1 ± 8.9 years) diagnosed with schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[25] criteria participated in this study. Exclusion criteria were current or past substance abuse, organic brain disease, or epilepsy. Subjects with severe liver or renal dysfunction or who had undergone electroconvulsive therapy within 90 days prior to this study were also excluded. The patients had been taking 1 oral antipsychotic drug at fixed dosage for at least 2 weeks before the start of this study (range, 2 weeks to 11 years; mean, 25 months). Seven patients took risperidone at 2 mg (n = 2), 4 mg (n = 4), and 6 mg (n = 1); 7 patients took olanzapine at 5 mg (n = 2), 10 mg (n = 3), 15 mg (n = 1), and 20 mg (n = 1); 4 patients took haloperidol at 6 mg (n = 2), 9 mg (n = 1), and 12 mg (n = 1); and 6 patients took sulpiride at 200 mg (n = 2), 400 mg (n = 2), 600 mg (n = 1), and 900 mg (n = 1). Antipsychotic treatment was continued during the performance of the PET scans using [^{11}C]FLB 457. The duration between PET scan and the last administration of antipsychotic drug was between 2 hours and 20 hours. Just before PET scan, venous blood samples were taken to measure the plasma concentration of prolactin.

After complete description of this study, written informed consent was obtained from all subjects. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiologic Sciences, Chiba, Japan. Data were collected between November 2001 and September 2007.

Positron Emission Tomography Procedure

A PET scanner system, ECAT EXACT HR+ (CTI-Siemens, Knoxville, Tennessee), was used for all subjects. A head fixation device was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source before each scan. Dynamic PET scan was performed for 90 minutes after intravenous bolus injection of 155.0–240.1 MBq (mean ± SD = 228.5 ± 72.5 MBq) of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 81.6–339.9 GBq/μmol (174.8 ± 63.4 GBq/μmol). Magnetic resonance images (MRIs) of the brain were acquired with 1.5 Tesla MRI, Gyroscan NT (Philips Medical Systems, Best, The Netherlands). T1-weighted images were obtained at 1-mm slices. All subjects were free of organic brain or pituitary lesions.

Data Analysis

All emission scan data were reconstructed with a Hanning filter. Regions of interest (ROIs) were defined for the pituitary, temporal cortex, and cerebellar cortex. The ROIs were drawn manually on PET images with reference to the individual magnetic resonance images. The values of ROIs for the right and left sides were averaged. The temporal cortex was used as the representative brain region because there was little difference in dopamine D_2 receptor occupancy among extrastriatal brain regions.[26] Binding potential (BP_{ND}) of dopamine D_2 receptors was calculated from the ratio of the area under the time-activity curve (AUC):

$$BP_{ND} = (AUC_{region} / AUC_{cerebellum}) - 1 \quad \text{(Equation 1)}.$$

The subscript "region" denotes the pituitary and temporal cortex. The cerebellum was used as reference tissue given its negligible density of dopamine D_2 receptors.[27] In this study, an integration interval of 60 to 90 minutes was used for the calculation of AUC.[20]

The receptor occupancy of antipsychotic drug is expressed as follows[14]:

$$\text{Occupancy (\%)} = (BP_{baseline} - BP_{drug}) / BP_{baseline} \times 100 \quad \text{(Equation 2)},$$

in which $BP_{baseline}$ is the baseline BP_{ND} in the drug-free state and BP_{drug} is BP_{ND} after the administration of antipsychotic drug. In the healthy subjects study, both BP_{ND} values obtained from each individual were used. In the patients study, the mean BP_{ND} of 15 age-matched healthy male subjects (age range, 21–49 years, mean ± SD = 34.2 ± 8.4 years) was used as $BP_{baseline}$ because of the lack of individual baseline BP_{ND} values. There was no difference in age between healthy subjects and patients (2-tailed *t* test; $P = .32$). There was no age effect of BP_{ND} in the temporal cortex ($P = .37$) and pituitary ($P = .61$) within this age range (21–49 years) of healthy subjects.

The relationship between receptor occupancy and antipsychotic drug dose can be expressed as follows[18,21]:

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

in which D is the dose of drug and ED_{50} is the dose required to induce 50% occupancy.

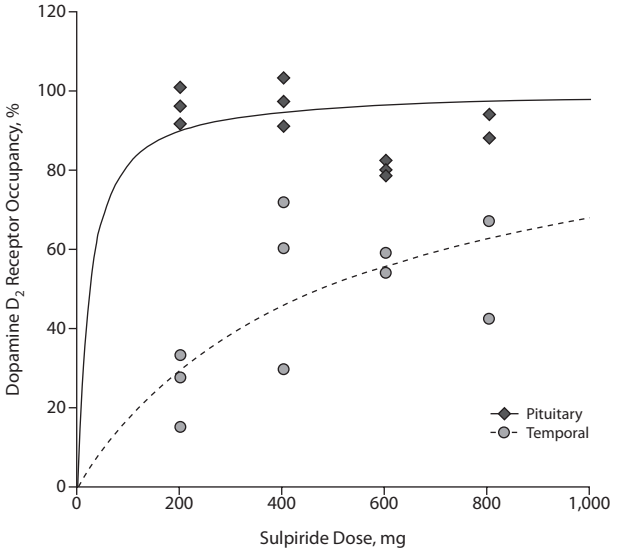
We calculated the ratio of drug concentration in the cerebral cortex to that in plasma (brain/plasma ratio; B/P ratio), which indicates the penetrating capability of antipsychotic drugs across the blood-brain barrier. Equation 3 can be rewritten as follows:

$$C = IC_{50} / ([100 / \text{Occupancy}] - 1) \quad \text{(Equation 4)},$$

in which C is the drug concentration in the brain or plasma. IC_{50} is the drug concentration required to induce 50% occupancy, reflecting the affinity of each antipsychotic drug to dopamine D_2 receptor, and, therefore, IC_{50} can be assumed

© Copyright 2010 Physicians Postgraduate Press, Inc.

Figure 1. Relationship Between Dose of Sulpiride and Dopamine D_2 Receptor Occupancy in the Pituitary or Temporal Cortex in Healthy Subjects[a]



[a]Dopamine D_2 receptors in the pituitary were almost fully occupied even at the lowest dose of sulpiride (200 mg), at which occupancy in the temporal cortex was around 25%. Curves were fitted according to this equation: Occupancy (%) = D / (D + ED_{50}) × 100. ED_{50} for the pituitary was 22.2 mg and 475.6 mg for the temporal cortex.

to be the same value between the pituitary and the temporal cortex. Because the pituitary exists outside the blood-brain barrier, the B/P ratio can be expressed as follows:

$$B/P\ ratio = C_{brain} / C_{pituitary} = ([100 / Occupancy_{pituitary}] - 1) / ([100/Occupancy_{temporal}] - 1) \quad \text{(Equation 5)},$$

in which $C_{pituitary}$ is the drug concentration in the vicinity of receptors in the pituitary, and C_{brain} is the drug concentration in the vicinity of receptors in the temporal cortex. $Occupancy_{pituitary}$ is the dopamine D_2 receptor occupancy in the pituitary, and $Occupancy_{temporal}$ is that in the temporal cortex. The B/P ratio of each antipsychotic drug was calculated.

Prolactin Measurement

The plasma concentration of prolactin was measured by chemiluminescent immunoassay at a commercial laboratory (SRL Inc, Tokyo, Japan). The normal range for males is 3.6–12.8 ng/mL. Values exceeding 12.8 ng/mL were defined as hyperprolactinemia.

Simulation Study

A simulation study was performed in order to estimate the relationship between the B/P ratio and prolactin. First, pituitary occupancy was calculated by Equation 5 according to changes in the B/P ratio when occupancy in the temporal cortex was set at 60%, 70%, and 80%, which was the range of clinical dosage.[12–14] Next, assumed prolactin values were estimated using linear regression obtained from the patients study. The measured prolactin values in patients (mean temporal cortex occupancy, 66.5 ± 13.9%) were plotted in this simulation graph against the mean B/P ratio of each antipsychotic drug.

Statistics

Correlations between plasma concentration of prolactin and dopamine D_2 receptor occupancy in the pituitary or temporal cortex by the 4 antipsychotic drugs were evaluated using Pearson correlation coefficient. The relationship between occupancy in the pituitary and hyperprolactinemia was evaluated using Fisher exact test. Group differences of B/P ratio among the 4 antipsychotics were evaluated by Kruskal-Wallis test. Multiple comparisons of B/P ratio between the respective antipsychotics were evaluated using the Mann-Whitney *U* test with Ryan method.

RESULTS

Study of Healthy Subjects Receiving Different Doses of Sulpiride

Dopamine D_2 receptor occupancy in the pituitary by sulpiride ranged from 78.4% to 103.2% (mean ± SD = 96.1 ± 4.6% for 200 mg, 97.1 ± 6.1% for 400 mg, 80.3 ± 1.9% for 600 mg, and 91.1 ± 4.2% for 800 mg), and the occupancy in the temporal cortex ranged from 15.2% to 71.9% (25.4 ± 9.3% for 200 mg, 54.0 ± 21.8% for 400 mg, 55.9 ± 2.9% for 600 mg, and 54.8 ± 17.5% for 800 mg) (Figure 1). ED_{50} for the pituitary was 22.2 mg and for the temporal cortex was 475.6 mg. The plasma concentration of prolactin ranged from 19.1 to 41.7 ng/mL. The plasma concentration of prolactin for all subjects reached the level of hyperprolactinemia.

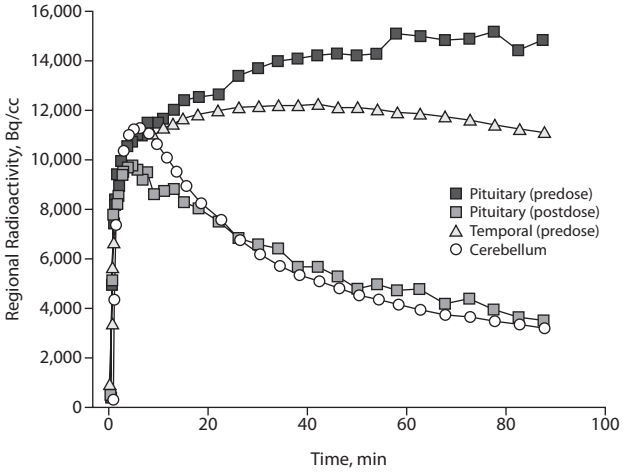
Figure 2 shows the mean values of the time-activity curves of the pituitary (predose and postdose of sulpiride), temporal cortex (predose), and cerebellum of the 11 healthy subjects. The curve of the pituitary at postdose was decreased to a level similar to that of the cerebellum.

Study of Patients Receiving Different Antipsychotics

Dopamine D_2 receptor occupancies in the pituitary by risperidone, olanzapine, haloperidol, and sulpiride were 49.2%–80.1%, 18.6%–79.5%, 27.2%–104.4%, and 68.9%–108.4%, respectively, and those in the temporal cortex were 53.4%–79.5%, 50.7%–76.2%, 66.9%–83.2%, and 26.9%–81.8%, respectively. Plasma concentrations of prolactin of patients with risperidone, olanzapine, haloperidol, and sulpiride were 8.9 to 39.9 ng/mL, 3.5 to 23.0 ng/mL, 4.7 to 22.7 ng/mL, and 34.7 to 57.4 ng/mL, respectively. The percentages of hyperprolactinemia of olanzapine, haloperidol, risperidone, and sulpiride were 29% (2/7), 50% (2/4), 86% (6/7), and 100% (6/6), respectively.

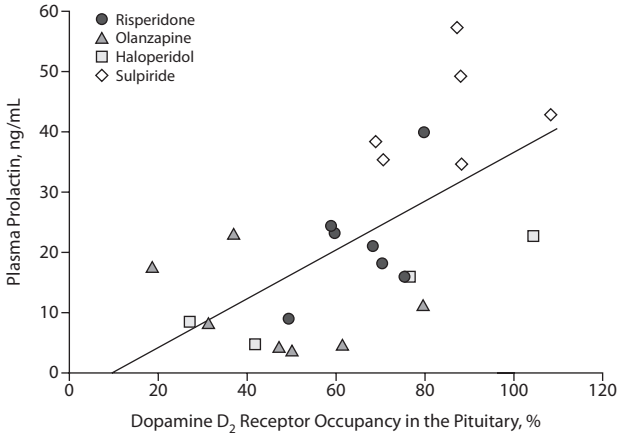
Significant positive correlation was observed between the plasma concentration of prolactin and dopamine D_2 receptor occupancy in the pituitary by the 4 antipsychotic drugs (Y = 0.41X – 4.0; $r = 0.62$; $P = .001$) (Figure 3). However, no correlation was found between the plasma concentration of prolactin and dopamine D_2 receptor occupancy in the temporal cortex by the 4 antipsychotic drugs ($r = -0.097$; $P = .65$) (Figure 4). When the threshold was set with every 10% of

Figure 2. Time-Activity Curves of the Pituitary (Predose and Postdose), Temporal Cortex (Predose), and Cerebellum in Mean Values of Eleven Healthy Subjects[a]



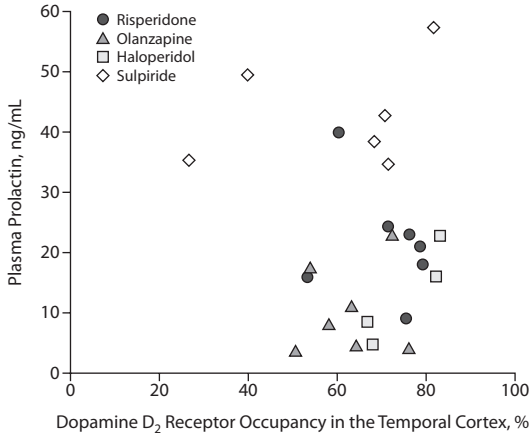
[a]In the pituitary of postdose, the mean value of all dosages was used. The postdose time-activity curve of the pituitary was decreased to a level similar to that of the cerebellum.

Figure 3. Relationship Between Dopamine D_2 Receptor Occupancy in the Pituitary and Plasma Concentration of Prolactin in Patients With Schizophrenia[a]



[a]Significant positive correlation was observed between the plasma concentration of prolactin and dopamine D_2 receptor occupancy in the pituitary by different doses of risperidone, olanzapine, haloperidol, and sulpiride ($Y = 0.41X - 4.0$; $P = .001$).

Figure 4. Relationship Between Dopamine D_2 Receptor Occupancy in the Temporal Cortex and Plasma Concentration of Prolactin in Patients With Schizophrenia[a]



[a]No correlation was observed between the plasma concentration of prolactin and dopamine D_2 receptor occupancy in the temporal cortex ($P = .65$).

occupancy in the pituitary, patients with hyperprolactinemia could be estimated using Fisher exact test at 50% with the lowest P value ($P = .005$).

The B/P ratio of the 4 antipsychotics differed significantly ($\chi^2_3 = 8.54$; $P = .036$). The mean ± SD B/P ratios of olanzapine, haloperidol, risperidone, and sulpiride were 2.70 ± 1.84, 2.40 ± 2.40, 1.61 ± 1.00, and 0.34 ± 0.42, respectively (Figure 5), the same order as the percentages of hyperprolactinemia. The B/P ratios were significantly different in olanzapine versus sulpiride ($U = 2$; $P = .007 < 0.05/6$) and risperidone versus sulpiride ($U = 4$; $P = .015 < 0.05/2$), but haloperidol versus sulpiride did not reach significance ($U = 6$; $P = .20$). Figure 6 shows the PET images of 1 healthy subject and 2 patients, 1 taking olanzapine and the other sulpiride. Sulpiride blocked dopamine D_2 receptors to a greater extent in the pituitary than in the temporal cortex, and olanzapine showed relatively less effect in the pituitary.

In the simulation study, drugs with a low B/P ratio induced a high prolactin level at clinical doses with 60%–80% of dopamine D_2 receptor occupancy in the temporal cortex. The measured prolactin values of patients also showed the same tendency (Figure 7). The simulated plasma prolactin level increased when the set value of occupancy in the temporal cortex was increased.

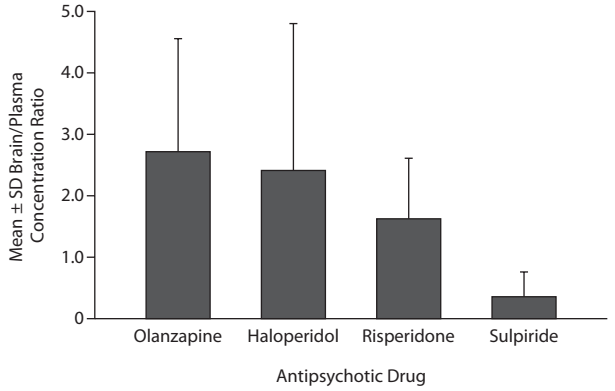
DISCUSSION

In the present study healthy subjects treated with different doses of sulpiride, a marked difference in dopamine D_2 receptor occupancy was confirmed between the pituitary and temporal cortex using the baseline of each. Dopamine D_2 receptors in the pituitary were almost fully occupied even at the lowest dose (200 mg), at which occupancy in the temporal cortex was around 25% (Figure 1). Lipophilicity is a major determinant of the penetrating ability into the brain.[28] Since the log P value of sulpiride is reported to be 0.42–1.31, the low brain uptake was considered to be due to lower lipophilicity.[29,30]

Although nonspecific binding in the pituitary may not be the same as that of the brain parenchyma, the fully occupied time-activity curve of the pituitary was at almost the same level as that of the cerebellum (Figure 2), suggesting that the cerebellum could be used as a measure of nonspecific binding in the pituitary. In the calculation of BP_{ND} in the pituitary, we used the AUC ratio method, which does not require the assumptions that are required for the simplified reference tissue model method (SRTM). The effect of the radiolabeled metabolite of [^{11}C]FLB 457 would be small for

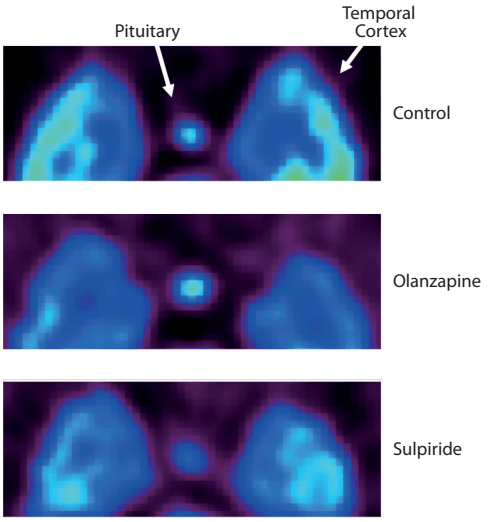
© Copyright 2010 Physicians Postgraduate Press, Inc.

Figure 5. Antipsychotic Drug Concentration Ratio in the Brain to Plasma (B/P ratio) of 4 Drugs in Patients With Schizophrenia[a]



[a]B/P ratios of olanzapine, haloperidol, risperidone, and sulpiride were mean ± SD = 2.70 ± 1.84, 2.40 ± 2.40, 1.61 ± 1.00, and 0.34 ± 0.42, respectively. B/P ratios were significantly different in olanzapine versus sulpiride ($P = .007$) and risperidone versus sulpiride ($P = .015$), but haloperidol versus sulpiride did not reach significance ($P = .20$).

Figure 6. Positron Emission Tomography Images of 1 Healthy Subject and 2 Patients Taking Olanzapine or Sulpiride[a]



[a]The 3 positron emission tomography images were axial slices at the pituitary and temporal cortex. High brightness indicates high binding of [^{11}C]FLB 457, meaning less occupied dopamine D_2 receptors. Sulpiride blocked dopamine D_2 receptors in the pituitary more preferentially than in the temporal cortex, whereas olanzapine showed relatively less occupied dopamine D_2 receptors in the pituitary.

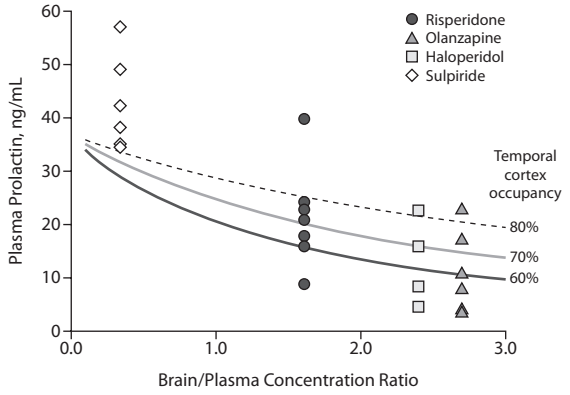
the measurement of dopamine D_2 receptors in the pituitary because a previous study indicated that a major metabolite of [^{11}C]FLB 457 had very low affinity for dopamine D_2 receptors.[16] The BP_{ND} values in the temporal cortex were measured by the same method. Binding potential in the extrastriatum by AUC ratio method showed good correlation with those by indirect kinetic method (reported value; $r = 0.96$).[20] Although some subjects did not reach equilibrium in the pituitary in this study, the mean value of BP_{ND} in the pituitary was 2.11, almost the same as the reported value in the temporal cortex (2.23) and less than that in the thalamus (3.67), suggesting that the equilibrium would be around the measured time range. Furthermore, the occupancies in the pituitary of patients (n = 24) calculated by the SRTM method showed good correlation with those by the AUC ratio method ($r = 0.94$, data not shown). These data suggested that the AUC ratio method can also be used for quantification of the pituitary.

The present study demonstrated that dopamine D_2 receptor occupancy in the pituitary by 4 antipsychotic drugs was significantly correlated with the plasma concentration of prolactin ($Y = 0.41X - 4.0$; $P = .001$) (Figure 3), but no such correlation was found in the temporal cortex (Figure 4). It has been reported that hyperprolactinemia was induced when dopamine D_2 receptor occupancy in the striatum exceeded 50% for raclopride[31] and 72% for haloperidol.[12] However, no correlation was reported between hyperprolactinemia and striatal or temporal cortex occupancy by amisulpride.[32] In this study using Fisher exact test, the patients with hyperprolactinemia could be estimated at 50% with the lowest P value ($P = .005$). This indicated that 50% of dopamine D_2 receptor occupancy in the pituitary might represent a threshold level of hyperprolactinemia.

The magnitude of hyperprolactinemia differs among antipsychotics. It has been reported that atypical antipsychotics showed a low risk of hyperprolactinemia as compared to typical antipsychotics.[1,5,7] Although olanzapine, clozapine, and quetiapine reportedly showed a relatively low risk,[5–8] risperidone and amisulpride, regarded as atypical antipsychotics, presented a high risk.[5–8,32] This difference was discussed in relation to the affinity to dopamine D_2 receptors.[6,8] Risperidone has relatively high affinity, whereas those of olanzapine, clozapine, and quetiapine are medium or low.[33] This order is apparently in accordance with the risk of hyperprolactinemia, although amisulpride has a high risk despite its medium affinity.[33] Thus, after all, the affinity for dopamine D_2 receptors could not conclusively explain the risk of hyperprolactinemia.

A previous animal study suggested that the dissociation between central and peripheral dopamine D_2 receptor occupancy could be a marker of prolactin elevation.[9] The reported ED_{50} ratios of the pituitary to the striatum were 654 for amisulpride, 11 for risperidone, and 0.7 for olanzapine, indicating that their respective permeabilities were low, medium, and high. In this study, we calculated the B/P ratio defined as the ratio of antipsychotic drug concentration at the temporal cortex receptor site to that at the pituitary receptor site to explain the ED_{50} difference between that in the pituitary and the temporal cortex. It was based on the assumption of fixed IC_{50}, although several factors should be considered concerning the IC_{50} determination. First, endogenous dopamine may affect the BP_{ND} values of [^{11}C]FLB 457. Some studies reported that dopamine manipulation such as amphetamine challenge did not change BP_{ND},[34–36] but other studies reported a different conclusion.[37–42] In this study, we assumed that, compared with amphetamine challenge, antipsychotic drug did not substantially change endogenous dopamine. Second, antipsychotic concentration change during the PET scan may affect the occupancy values

Figure 7. Simulated Curve Between Antipsychotic Drug Concentration Ratio in the Brain to Plasma (B/P ratio) and Estimated Prolactin Level at Clinical Dosage[a]



[a]Drug with a low B/P ratio induces a high prolactin level at clinical dosage. Occupancy in the temporal cortex was set at 60%–80%. Prolactin values measured in patients were also plotted against mean B/P ratio, which can be a characteristic index of each antipsychotic drug.

according to a previous study.[24] Our previous studies reported that there was no regional difference of dopamine D_2 receptor occupancy between the striatum and extrastriatum.[43] Moreover, dopamine D_2 receptor densities showed similar values between the temporal cortex and pituitary ($B_{max} = 0.4$ and 1.3 pmol/g tissue, respectively).[15] In this study, the drug washout rate could be ignored because patient treatment was in the steady-state and receptor densities were close between the 2 sites. Taken together, we assumed that IC_{50} values were the same between the pituitary and the temporal cortex, and that the antipsychotic drug concentration difference could be estimated.

The order of the B/P ratio in our results was consistent with that of the ED_{50} ratio in the above-mentioned animal study. The B/P ratio can be the characteristic index of antipsychotic drugs. The concentration of sulpiride in the temporal cortex was one-third of that in the pituitary, while those of olanzapine and haloperidol were about double or triple. Sulpiride had significantly low permeability compared to risperidone ($P = .015$) and olanzapine ($P = .007$), indicating the high risk of hyperprolactinemia for sulpiride.[5] Although no significant difference of B/P ratio between haloperidol and sulpiride was observed, possible reasons were small sample size and large SD. The order of the B/P ratio was the same as the percentage of hyperprolactinemia in this study. In the simulation study, a drug with low B/P ratio induced a high prolactin level at clinical dosage with 60%–80% of dopamine D_2 receptor occupancy in the temporal cortex (Figure 7). The measured prolactin values of patients showed a similar tendency to the simulated ones. Thus, the B/P ratio seems to be a useful index for predicting the risk of each antipsychotic drug for hyperprolactinemia.

Brain permeability differences are the result of several factors. The Log *P* values of risperidone, olanzapine, and haloperidol are 3.04, 2.89, and 3.36–3.52, respectively,[30,44,45] and the higher permeability of risperidone, olanzapine, and haloperidol compared to sulpiride (or amisulpride; Log $P = 1.10–1.70$[29,45]) can be ascribed to high lipophilicity. However, risperidone, in fact, has a slightly higher Log *P* value than olanzapine despite its slightly lower permeability, a seeming contradiction explainable by the fact that risperidone is reportedly a substrate of P-glycoprotein, one of the efflux transporters at the blood-brain barrier.[46,47]

There were several confounding factors in this study. In the patients study, we used the mean BP_{ND} of healthy control subjects as baseline because previous studies showed no differences in dopamine D_2 receptors in the temporal cortex between patients and healthy subjects[17,19] or lower binding in patients.[48,49] A variety of baseline BP_{ND} values can lead to large SD of occupancy or B/P ratio. For example, if BP_{base} changes by ±15%,[17] the calculated 50% occupancy could be changed from 41% to 57%. The variety would affect the statistics significantly, especially with the small number of subjects like the haloperidol cases. Furthermore, possible change in the pituitary of patients with schizophrenia[50] could lead to potential errors in the estimation of occupancy values.

In conclusion, dopamine D_2 receptor occupancies in the pituitary by 4 different antipsychotics were well correlated with the plasma concentration of prolactin. The B/P ratios of the 4 antipsychotics were significantly different. The magnitude of hyperprolactinemia of various antipsychotics can be predicted by the B/P ratio, which indicates the permeability of antipsychotics into the brain. Thus, especially in the area of new drug development, the B/P ratio of each antipsychotic drug might prove to be useful for the early evaluation of the risk of hyperprolactinemia.

Drug names: clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

Author affiliations: Molecular Neuroimaging Group, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan (Drs Arakawa, Okumura, Ito, A. Takano, Takahashi, H. Takano, Maeda, and Suhara); and Department of Neuropsychiatry, Nippon Medical School, Tokyo, Japan (Drs Arakawa, Okumura, and Okubo).

Potential conflicts of interest: The authors have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This study was supported by a consignment expense for the Molecular Imaging Program on "Research Base for Positron Emission Tomography (PET) Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government.

Role of sponsor: The sponsors of the study had no role in the study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Acknowledgment: We thank Mr Katsuyuki Tanimoto, BS, Mr Takahiro Shiraishi, BS, Mr Akira Ando, BS, and Mr Toshio Miyamoto, BS, from the National Institute of Radiological Science in Chiba, Japan, for their assistance in performing the PET experiments, Mr Takashi Okauchi, BS, from the National Institute of Radiological Science in Chiba, Japan, for advice on the statistics, and Ms Yoshiko Fukushima, BS, from the National Institute of Radiological Science in Chiba, Japan, for her help as clinical research coordinator at the National Institute of Radiological Sciences. We also thank Dr Jun Kosaka, MD, from the Sobu Hospital in Chiba, Japan, and Dr Amane Tateno, MD, PhD, Dr Mizuho Sekine, MD, and Dr Hajime Fukuta, MD, from the Nippon Medical School in Tokyo, Japan, for their clinical support. All acknowledged individuals have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

© Copyright 2010 Physicians Postgraduate Press, Inc.

REFERENCES

1. Hamner M. The effects of atypical antipsychotics on serum prolactin levels. *Ann Clin Psychiatry*. 2002;14(3):163–173.
2. Hummer M, Huber J. Hyperprolactinaemia and antipsychotic therapy in schizophrenia. *Curr Med Res Opin*. 2004;20(2):189–197.
3. O'Keane V, Meaney AM. Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia? *J Clin Psychopharmacol*. 2005;25(1):26–31.
4. Lieberman JA, Stroup TS, McEvoy JP, et al.Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
5. Markianos M, Hatzimanolis J, Lykouras L. Neuroendocrine responsivities of the pituitary dopamine system in male schizophrenic patients during treatment with clozapine, olanzapine, risperidone, sulpiride, or haloperidol. *Eur Arch Psychiatry Clin Neurosci*. 2001;251(3):141–146.
6. Melkersson K. Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. *J Clin Psychiatry*. 2005;66(6):761–767.
7. Montgomery J, Winterbottom E, Jessani M, et al. Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment. *J Clin Psychiatry*. 2004;65(11):1491–1498.
8. Volavka J, Czobor P, Cooper TB, et al. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychiatry*. 2004;65(1):57–61.
9. Kapur S, Langlois X, Vinken P, et al. The differential effects of atypical antipsychotics on prolactin elevation are explained by their differential blood-brain disposition: a pharmacological analysis in rats. *J Pharmacol Exp Ther*. 2002;302(3):1129–1134.
10. Jaber M, Robinson SW, Missale C, et al. Dopamine receptors and brain function. *Neuropharmacology*. 1996;35(11):1503–1519.
11. Freeman ME, Kanyicska B, Lerant A, et al. Prolactin: structure, function, and regulation of secretion. *Physiol Rev*. 2000;80(4):1523–1631.
12. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D_2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000;157(4):514–520.
13. Nordström AL, Farde L, Wiesel FA, et al. Central D_2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry*. 1993;33(4):227–235.
14. Farde L, Nordström AL, Wiesel FA, et al. Positron emission tomographic analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. *Arch Gen Psychiatry*. 1992;49(7):538–544.
15. Kessler RM, Whetsell WO, Ansari MS, et al. Identification of extrastriatal dopamine D_2 receptors in post mortem human brain with [^{125}I]epidepride. *Brain Res*. 1993;609(1–2):237–243.
16. Halldin C, Farde L, Högberg T, et al. Carbon-11-FLB 457: a radioligand for extrastriatal D_2 dopamine receptors. *J Nucl Med*. 1995;36(7):1275–1281.
17. Suhara T, Okubo Y, Yasuno F, et al. Decreased dopamine D_2 receptor binding in the anterior cingulate cortex in schizophrenia. *Arch Gen Psychiatry*. 2002;59(1):25–30.
18. Takano A, Suhara T, Yasuno F, et al. The antipsychotic sultopride is overdosed—a PET study of drug-induced receptor occupancy in comparison with sulpiride. *Int J Neuropsychopharmacol*. 2006;9(5):539–545.
19. Talvik M, Nordström AL, Olsson H, et al. Decreased thalamic D_2/D_3 receptor binding in drug-naive patients with schizophrenia: a PET study with [^{11}C]FLB 457. *Int J Neuropsychopharmacol*. 2003;6(4):361–370.
20. Ito H, Sudo Y, Suhara T, et al. Error analysis for quantification of [^{11}C]FLB 457 binding to extrastriatal D_2 dopamine receptors in the human brain. *Neuroimage*. 2001;13(3):531–539.
21. Arakawa R, Ito H, Takano A, et al. Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine D_2 receptor occupancy in patients with schizophrenia. *Psychopharmacology (Berl)*. 2008;197(2):229–235.
22. Mukherjee J, Christian BT, Dunigan KA, et al. Brain imaging of ^{18}F-fallypride in normal volunteers: blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. *Synapse*. 2002;46(3):170–188.
23. Bergström M, Muhr C, Lundberg PO, et al. PET as a tool in the clinical evaluation of pituitary adenomas. *J Nucl Med*. 1991;32(4):610–615.
24. Kegeles LS, Slifstein M, Frankle WG, et al. Dose-occupancy study of striatal and extrastriatal dopamine D_2 receptors by aripiprazole in schizophrenia with PET and [^{18}F]fallypride. *Neuropsychopharmacology*. 2008;33(13):3111–3125.
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
26. Yasuno F, Suhara T, Okubo Y, et al. Dose relationship of limbic-cortical D_2-dopamine receptor occupancy with risperidone. *Psychopharmacology (Berl)*. 2001;154(1):112–114.
27. Suhara T, Sudo Y, Okauchi T, et al. Extrastriatal dopamine D_2 receptor density and affinity in the human brain measured by 3D PET. *Int J Neuropsychopharmacol*. 1999;2(2):73–82.
28. Bickel U. How to measure drug transport across the blood-brain barrier. *NeuroRx*. 2005;2(1):15–26.
29. Mannhold R, Cruciani G, Dross K, et al. Multivariate analysis of experimental and computational descriptors of molecular lipophilicity. *J Comput Aided Mol Des*. 1998;12(6):573–581.
30. Hansch C, Sammes P, Taylor J. *Comprehensive Medicinal Chemistry*. Oxford, UK: Pergamon Press; 1990.
31. Nordström AL, Farde L. Plasma prolactin and central D_2 receptor occupancy in antipsychotic drug-treated patients. *J Clin Psychopharmacol*. 1998;18(4):305–310..
32. Bressan RA, Erlandsson K, Spencer EP, et al. Prolactinemia is uncoupled from central D_2/D_3 dopamine receptor occupancy in amisulpride treated patients. *Psychopharmacology (Berl)*. 2004;175(3):367–373.
33. Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry*. 2002;47(1):27–38.
34. Okauchi T, Suhara T, Maeda J, et al. Effect of endogenous dopamine on endogenous dopamine on extrastriated [^{11}C]FLB 457 binding measured by PET. *Synapse*. 2001;41(2):87–95.
35. Tsukada H, Miyasato K, Nishiyama S, et al. Nicotine normalizes increased prefrontal cortical dopamine D_1 receptor binding and decreased working memory performance produced by repeated pretreatment with MK-801: a PET study in conscious monkeys. *Neuropsychopharmacology*. 2005;30(12):2144–2153.
36. Aalto S, Hirvonen J, Kaasinen V, et al. The effects of *d*-amphetamine on extrastriatal dopamine D_2/D_3 receptors: a randomized, double-blind, placebo-controlled PET study with [^{11}C]FLB 457 in healthy subjects. *Eur J Nucl Med Mol Imaging*. 2009;36(3):475–483.
37. Chou YH, Halldin C, Farde L. Effect of amphetamine on extrastriatal D_2 dopamine receptor binding in the primate brain: a PET study. *Synapse*. 2000;38(2):138–143.
38. Tsukada H, Nishiyama S, Fukumoto D, et al. Chronic NMDA antagonism impairs working memory, decreases extracellular dopamine, and increases D_1 receptor binding in prefrontal cortex of conscious monkeys. *Neuropsychopharmacology*. 2005;30(10):1861–1869.
39. Aalto S, Brück A, Laine M, et al. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D_2 receptor ligand [^{11}C]FLB 457. *J Neurosci*. 2005;25(10):2471–2477.
40. Aalto S, Ihalainen J, Hirvonen J, et al. Cortical glutamate-dopamine interaction and ketamine-induced psychotic symptoms in man. *Psychopharmacology (Berl)*. 2005;182(3):375–383.
41. Montgomery AJ, Asselin MC, Farde L, et al. Measurement of methylphenidate-induced change in extrastriatal dopamine concentration using [^{11}C]FLB 457 PET. *J Cereb Blood Flow Metab*. 2007;27(2):369–377.
42. Narendran R, Frankle WG, Mason NS, et al. Positron emission tomography imaging of amphetamine-induced dopamine release in the human cortex: a comparative evaluation of the high affinity dopamine D2/3 radiotracers [^{11}C]FLB 457 and [^{11}C]fallypride. *Synapse*. 2009;63(6):447–461.
43. Ito H, Arakawa R, Takahashi H, et al. No regional difference in dopamine D_2 receptor occupancy by the second-generation antipsychotic drug risperidone in humans: a positron emission tomography study. *Int J Neuropsychopharmacol*. 2009;12(5):667–675.
44. Mannens G, Meuldermans W, Snoeck E, et al. Plasma protein binding of risperidone and its distribution in blood. *Psychopharmacology (Berl)*. 1994;114(4):566–572.
45. El Ela AA, Härtter S, Schmitt U, et al. Identification of P-glycoprotein substrates and inhibitors among psychoactive compounds—implications for pharmacokinetics of selected substrates. *J Pharm Pharmacol*. 2004;56(8):967–975.
46. Higgins CF. Multiple molecular mechanisms for multidrug resistance transporters. *Nature*. 2007;446(7137):749–757.
47. Boulton DW, DeVane CL, Liston HL, et al. In vitro P-glycoprotein affinity for atypical and conventional antipsychotics. *Life Sci*. 2002;71(2):163–169.
48. Buchsbaum MS, Christian BT, Lehrer DS, et al. D_2/D_3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. *Schizophr Res*. 2006;85(1–3):232–244.
49. Tuppurainen H, Kuikka J, Viinamäki H, et al. Extrastriatal dopamine D 2/3 receptor density and distribution in drug-naive schizophrenic patients. *Mol Psychiatry*. 2003;8(4):453–455.
50. Dean B, Pavey G, Scarr E, et al. Measurement of dopamine D_2-like receptors in postmortem CNS and pituitary: differential regional changes in schizophrenia. *Life Sci*. 2004;74(25):3115–3131.