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Atypicality of Several Antipsychotics on the Basis of In Vivo Dopamine-D_2 and Serotonin-5HT_2 Receptor Occupancy

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An in vivo receptor binding technique was used to evaluate the binding profiles of typical and atypical antipsychotic drugs to striatal dopamine-D_2 and frontal serotonin-5-HT_2 receptors in a rat brain using more specific ligands than those previously employed. [^{3}H]-YM-09151-2 or [^{3}H]-ketanserin was injected into the tail vein 10 minutes after administration of test drugs. One hour after the ligand injection, radioactivities in the striatum, frontal cortex, and cerebellum were counted to obtain receptor occupancies by the test drugs. Higher ratios of potency in occupying 5-HT_2 versus D_2 receptors were found for clozapine, RMI-81512, and tiospirone compared to haloperiodol and pimozide. Zotepine, mosapramine, and clocapramine produced ratios that fall between these two groups. Chlorpromazine was exceptional as a typical antispychotic by these criteria. Relatively strong antagonism of 5-HT_2 receptors by atypical antipsychotics was confirmed by this in vivo measure of receptor binding using more selective ligands than those used in previous studies.
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KEY WORDS: *Atypical antipsychotic drugs; D_2 receptors; 5-HT_2 receptors; Receptor binding study; In vivo*

The mode of action of antipsychotic drugs has been discussed in relation to their potency to block central dopamine-D_2 receptors (Creese et al. 1976; Seeman et al. 1976). The so-called "typical" antipsychotic drugs have been shown to produce catalepsy in rats (Moore and Gershon 1989) and often, extrapyramidal side effects (EPS) in patients (Sovner and DiMascio 1978), by blocking the nigrostriatal dopamine system. "Atypical" antipsychotic drugs, on the other hand, are less likely to produce disturbances of EPS or elevation of serum prolactin (Young and Meltzer 1980; Porsolt and Jafre 1981; Neale et al. 1983), and demonstrate favorable clinical efficacy for both positive and negative symptoms of patients who are resistant to treatment with typical antipsychotics (Kane et al. 1988).

Since a relatively high affinity for serotonin$_2$ (5-HT_2) receptors of atypical antipsychotic drugs was postulated by Meltzer et al. (1989a, b), a number of studies to test this hypothesis have been performed in laboratory animals (Leysen et al. 1992; Matsubara et al. 1992; Stockmeier et al. 1993) and in human PET measurement (Nordstrom et al. 1993; Nyberg et al. 1993). We have previously demonstrated that the atypical antipsychotic drugs clozapine, RMI-81582, and risperidone show relatively higher 5-HT_2 to D_2 ratios of in vivo receptor affinities than haloperidol, measuring time courses of a receptor occupancy by single doses of these drugs (Sumiyoshi et al. 1993, 1994a, b).

In the present study, we used [^{3}H]-YM-09151-2 and

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[^{3}H]-ketaserin, selective ligands for D_2 and 5-HT_2 receptors, respectively (Laduron et al. 1982; Niznik et al. 1985; Terai et al. 1989), to measure the in vivo affinities of several antipsychotic drugs to these receptors by analyzing receptor occupancy. The test compounds include the new antipsychotic drug Y-516 (mosapramine) and clocapramine, iminodibenzyl derivatives that have been shown to exert favorable clinical effect on schizophrenic patients (Yamagami et al. 1988; Asano et al. 1992). The "atypicality" of these iminodibenzyls is also determined on the basis of in vivo D_2 and 5-HT_2 receptor occupancy in comparison with traditional typical and atypical antipsychotics.

MATERIALS AND METHODS

In Vivo Receptor Binding

Male Wistar rats (210 to 240 g; Sankyo Laboratory, Toyama, Japan) were housed in a temperature-controlled room with a 12-hour dark/light cycle (lights on at 8:30) and had free access to food and water. In vivo binding of [^{3}H]-YM-09151-2 (specific activity 3.22 TBq/mmol) to D_2 receptors or [^{3}H]-ketanserin (specific activity 2.22 TBq/mmol) to 5-HT_2 receptors was measured according to a method previously reported (Sumiyoshi et al. 1993, 1994a, b). For the kinetic study, [^{3}H]-YM-09151-2 or [^{3}H]-ketanserin (1540 to 1680 kBq/kg body weight) were injected into the lateral tail vein of rats that had received an intraperitoneal injection of a vehicle (dimethyl-sulfoxide, Wako Chemical Co., Oaska, Japan, 1 ml/kg), 10 minutes before. The rats were sacrificed by decapitation at 15, 30, 45, 60, 120, or 240 minutes after the injections of ligands. For competition studies, rats were pretreated with an intraperitoneal injection of varying doses of antipsychotic drugs or the same volume (0.21 to 0.24 ml) of the corresponding vehicle (dimethyl-sulfoxide), 10 minutes prior to the injection of [^{3}H]-YM-09151-2 or [^{3}H]-ketanserin. Based on results of the kinetic study, the rats were decapitated 60 minutes after the ligand injection. The brains were rapidly removed and dissected into cerebellum, striatum, frontal cortex, and the rest of the brain. After weighing, each region of the brain was solubilized with a tissue solubilizer (Soluene 350, Packard Co., CN) by incubation for 2 to 3 hours at 50°C. A scintillation cocktail (Aquasol 2, New England Nuclear) was added to the solubilized tissues adjusted to pH 7.0 with 0.5 N HCl solution (for inhibition of pseudo-fluorescence). After 12 to 24 hours, the radioactivity concentrations in the tissues were counted with a liquid scintillation counter (LSC-1000, Aloka Co., Tokyo, Japan) and the values, expressed as %dose/g tissue, were calculated. Receptor occupancy was determined by a modification of the method of former reports (Geoders and Kuhar 1985; Miller et al. 1987): percent occupancy $\Phi = [1-(X_D-X_{nD})/(X_S-X_{nS}] \times 100$ (%), where each abbreviation represents the radioactivity (%dose/g tissue) of X_D, striatum, or frontal cortex of drug-treated rats; X_{nD}, cerebellum of drug-treated rats; X_S, striatum or frontal cortex of vehicle-treated rats; and X_{nS}, cerebellum of vehicle-treated rats.

Data Analysis

Dose-response competition curves were analyzed with the minimal-square method (Paalzow and Edlund 1979) and DE_{50} (mg/kg) values reflecting binding potencies of the test drugs were calculated. The ED_{50} values were then transformed into (−)log of the ED_{50} (mol/kg) (pED_{50}) to compare the receptor binding potencies of the test drugs in the present study with those of Stockmeier et al. (1993).

Drugs

[^{3}H]-YM-09151-2 (specific activity 3.22 TBq/mmol) and [^{3}H]-ketanserin (specific activity 2.22 TBq/mmol) were purchased from DuPont New England Nuclear Corporation (Boston, MA). The following compounds were generously supplied by the manufacturers: haloperidol (Dainippon Pharmaceutical Co., Osaka, Japan); clozapine (Sandoz Ltd., Basel, Switzerland); RMI-81582 (Marion Merrill Dow Pharmaceuticals, Cincinnati, OH); tiospirone (Bristol-Myers-Squibb, Wallingford, CT); chlorpromazine, mosapramine, clocapramine (Yoshitomi Pharmaceutical Ltd., Osaka, Japan); zotepine, pimozide (Fujisawa Pharmaceutical Co., Osaka, Japan).

RESULTS

The values of radioactivity in each brain region at the different time intervals after the injection of [^{3}H]-YM-09151-2 are shown in Figure 1. A relatively large amount of [^{3}H]-YM-09151-2 accumulates in the striatum as compared to the cerebellum. For [^{3}H]-ketanserin-treated rats, the values in the frontal cortex continued to be higher than those in the cerebellum, as shown in Figure 2. In the following drug competition studies, rats were sacrificed 60 minutes after the injection of radioligand, based on stable receptor occupancies by drugs at this time point as reported in our previous studies (Sumiyoshi et al. 1993, 1994a, b). Figures 3 to 10 show the occupancy of D_4 and 5-HT_2 receptors following various doses of typical antipsychotic drugs, pimozide and chlorpromazine; atypical antipsychotic drugs, clozapine, RMI-81582 and tiospirone; other drugs, zotepine, mosapramine and clocapramine. The dose-occupancy curves of haloperidol were reported elsewhere (Sumiyoshi et al. 1994a). Based on these occupancy curves, the ED_{50} values (mg/kg) of the test compounds for the in vivo occupancy of striatal D_2 and

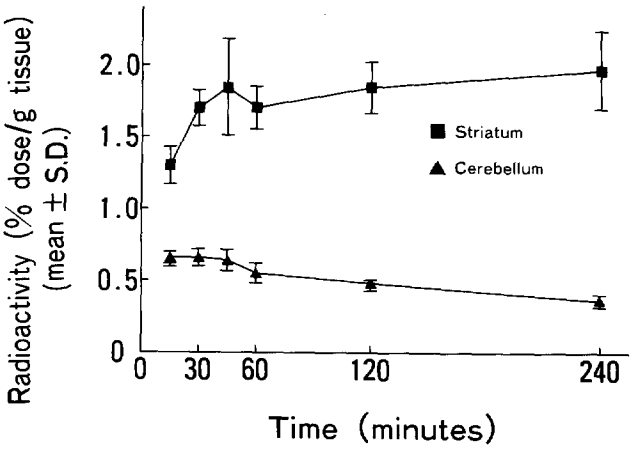

Figure 1. Kinetics of [^{3}H]-YM-09151-2 binding in vivo in rat brain. Rats were injected with [^{3}H]-YM-09151-2 (1540 to 1680 kBq/kg body weight) at time zero and killed at various times after injection. Values represent the mean ± SD of five rats at each time point.

frontal 5-HT$_2$ receptors are calculated (Table 1). The average ability of typical antipsychotic drugs to prevent the accumulation of [^{3}H]-YM-09151-2 in the striatum is more potent than for atypical antipsychotic drugs, except for tiospirone, revealing high affinity for [^{3}H]-YM-09151-2 labeled sites. In contrast, atypical antipsychotics are more potent than typical antipsychotics in preventing the accumulation of [^{3}H]-ketanserin in the frontal cortex. Chlorpromazine has a relatively high affinity for [^{3}H]-ketanserin labeled sites in the typical antipsychotic group. The ratios of ED$_{50}$ values of occupancy at 5-HT$_2$ versus D$_2$ receptors are also shown in the Table 1. Typical antipsychotics haloperidol and pimozide are slightly more potent in occupying D$_2$ than 5-HT$_2$ receptors. By contrast, atypical antipsychotics clozapine and RMI-81582 have a greater potency in occupying

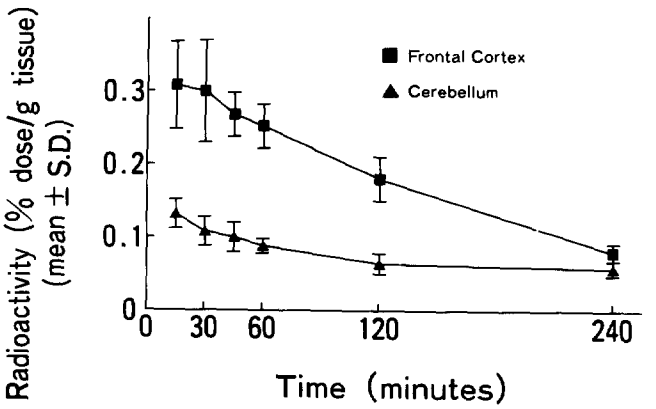

Figure 2. Kinetics of [^{3}H]-ketanserin binding in vivo in rat brain. Rats were injected with [^{3}H]-ketanserin (1540 to 1680 kBq/kg body weight) at time zero and killed at various times after injection. Values represent the mean ± SD of five rats at each time point.

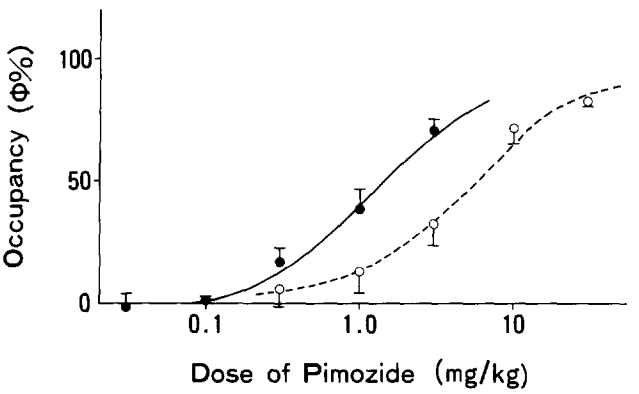

Figure 3. Occupancy (Φ%) of striatal D$_2$ and frontal 5-HT$_2$ receptors in rat brain with various doses of pimozide. [^{3}H]-YM-09151-2 or [^{3}H]-ketanserin (1540 to 1680 kBq/kg body weight) was injected into a tail vein at 10 minutes after administration (IP) with various doses of pimozide. Sixty minutes after the ligand injection, radioactivity in the striatum, frontal cortex, and cerebellum was counted. Each point represents the mean ± SE (n = 4 to 5). $\Phi = [1-(X_D-X_{nD})/(X_s-X_{ns})] \times 100$ (%), where each abbreviation represents radioactivity (%dose/g tissue) of X_D, striatum or frontal cortex of drug-treated rat; X_{nD}, cerebellum of drug-treated rat; X_S, striatum or frontal cortex of vehicle-treated rat; X_{nS}, cerebellum of vehicle-treated rat. The dose-response curves were analyzed with a minimal-square method. ● ●, D$_2$; ○ ○, 5-HT$_2$ receptors. (ordinate, occupancy for D$_2$ and 5-HT$_2$ receptors; abscissa, dose of pimozide).

5-HT$_2$ than D$_2$ receptors. The ratios of occupancy at 5-HT$_2$ versus D$_2$ receptors for zotepine, mosapramine, and clocapramine fall somewhere between those two categories. Chlorpromazine and tiospirone are exceptional among typical and atypical antipsychotics: chlorpromazine has a four- to fivefold greater potency in occupying 5-HT$_2$ than D$_2$ receptors, and tiospirone has only a slightly higher affinity for 5-HT$_2$ than D$_2$ receptors within the same order.

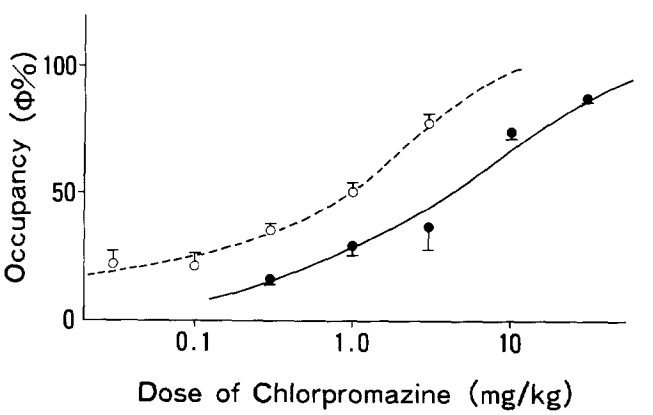

Figure 4. Occupancy (Φ%) of striatal D$_2$ and frontal 5-HT$_2$ receptors in rat brain with various doses of chlorpromazine. ● ●, D$_2$; ○ ○, 5-HT$_2$ receptors. (ordinate, occupancy for D$_2$ and 5-HT$_2$ receptors; abscissa, dose of chlorpromazine).

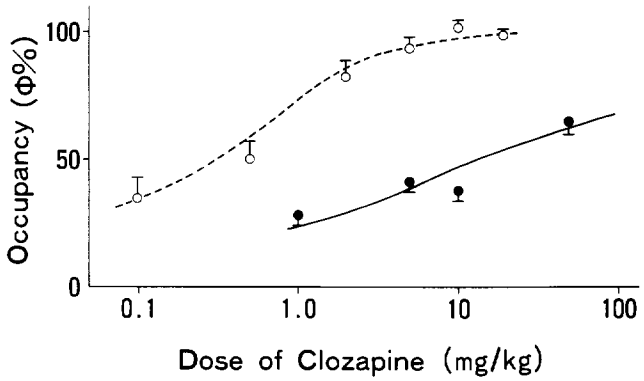

Figure 5. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of clozapine. ● ●, D_2; ○ ○, 5-HT_2 receptors. (ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of clozapine).

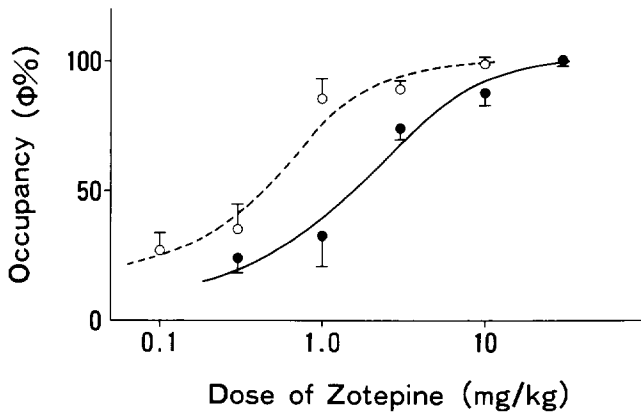

Figure 8. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of zotepine. ● ●, D_2; ○ ○, 5-HT_2 receptors. (ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of zotepine).

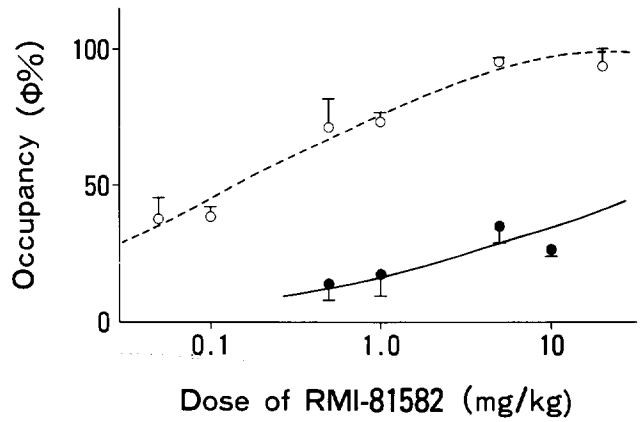

Figure 6. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of RMI-81582. ● ●, D_2; ○ ○, 5-HT_2 receptors. (ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of RMI-81582).

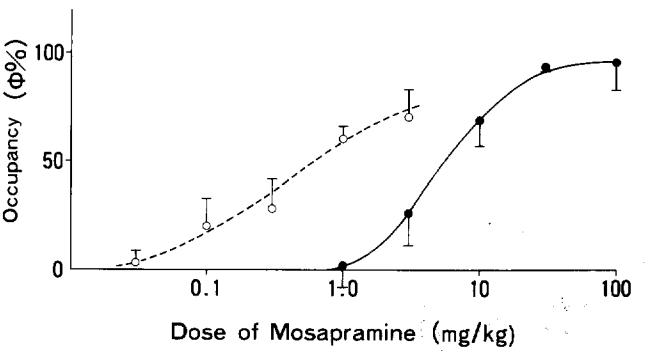

Figure 9. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of mosapramine. ● ●, D_2; ○ ○, 5-HT_2 receptors. (ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of mosapramine).

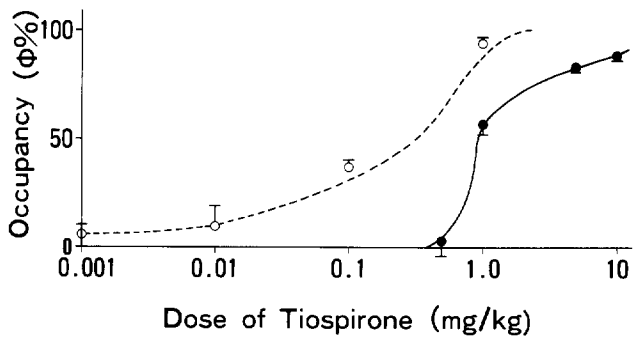

Figure 7. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of tiospirone. ● ●, D_2; ○ ○, 5-HT_2 receptors. (ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of tiospirone).

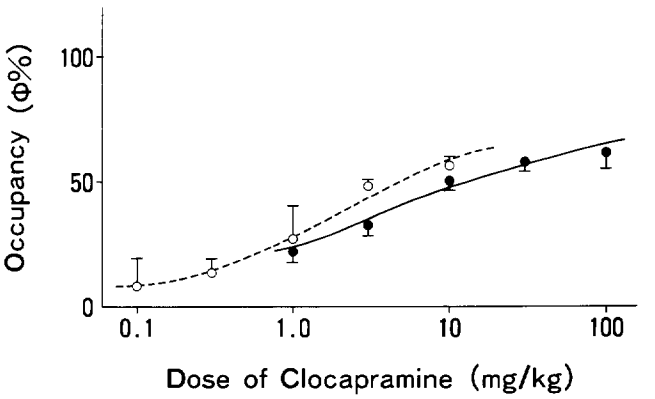

Figure 10. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of clocapramine. ● ●, D_2; ○ ○, 5-HT_2 receptors. (ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of clocapramine).

Table 1. ED50 Values for Receptor Occupancy

	D2	5-HT2	D2/5-HT2
Haloperidol	1.4	1.7	0.82
Pimozide	1.5	6.4	0.23
Chlorpromazine	4.6	1	4.6
Clozapine	14.6	0.3	49
RMI-81582	53	0.2	265
Tiospirone	0.9	0.3	3
Zotepine	1.7	0.4	4.3
Mosapramine	5.2	0.7	7.4
Clocapramine	14.5	4.9	3

Values are expressed as mg/kg, IP.

Table 2. Comparisons of (−)log of the ED50 Values (mol/kg)

	D2	5-HT2	5-HT2-D2
Haloperidol	5.44 (6.5)	5.33 (5.4)	−0.11 (−1.1)
Chlorpromazine	4.89 (5.4)	5.57 (6.0)	0.68 (0.6)
Clozapine	4.35 (4.3)	6.0 (5.6)	1.63 (1.3)
RMI-81582	3.77 (4.4)	6.3 (5.5)	2.53 (1.1)
Tiospirone	5.76 (5.9)	6.21 (6.5)	0.44 (0.6)
Zotepine	5.29 (5.1)	5.89 (6.1)	0.60 (1.0)

Data from Stockmeier et al. (1993) in parentheses.

To compare the present results with the former study (Stockmeier et al. 1993), the ED_{50} values (mg/kg) for occupying D_2 and 5-HT_2 receptors and their ratios of haloperidol, chlorpromazine, clozapine, RMI-81582, tiospirone, and zotepine were converted into (−)log ED_{50} (mol/kg) (pED_{50}, Table 2). The values in parentheses show the in vivo pED_{50}'s of Stockmeier et al. (1993). Strong correlations were obtained between the results of the two studies for D_2 receptor occupancy (Pearson's correlation coefficient, $R = 0.84$) and for the ratios of occupancy at 5-HT_2 versus D_2 receptors ($R = 0.71$), but not for 5-HT_2 receptor occupancy ($R = 0.31$).

DISCUSSION

Various studies have recently evaluated the in vivo receptor binding potency of antipsychotic drugs. Thus, Bischoff (1992), Leysen et al. (1992), and Stockmeier et al. (1993) have measured in vivo D_2 and 5-HT_2 receptor occupancy by typical and atypical antipsychotic drugs with laboratory animals. The latter two studies confirmed relatively strong 5-HT_2 receptor affinities of atypical antipsychotic drugs in comparison with typical ones in vivo. Moreover, central 5-HT_2 receptor occupancy of clozapine (Nordström et al. 1993) and risperidone (Nyberg et al. 1993) was recently reported even with human PET studies. These former studies utilized radio-labeled spiperone or its derivatives for labeling both the striatal D_2 and the cortical 5-HT_2 receptors at the same time. In contrast, we applied [^{3}H]-YM-09151-2 and [^{3}H]-ketanserin to label striatal D_2 and cortical 5-HT_2 receptors individually. As to the specificity of these ligands, radioactive derivatives of YM-09151-2 and ketanserin were reported to bind selectively in vivo to D_2 (Hatano et al. 1989) and 5-HT_2 (Laduron et al. 1982) receptors, respectively. Because the striatum is low in 5-HT_{1A} receptor sites, the binding of [^{3}H]-YM-09151-2 in the striatum does not appear to represent a significant 5-HT_{1A} site. The effective radioactivities counted both in [^{3}H]-YM-09151-2- and [^{3}H]-ketanserin-treated rats brains (Figures 1 and 2) made a basis for calculating receptor occupancies by the test drugs for striatal D_2 and frontal 5-HT_2 receptors.

Atypical antipsychotic drugs clozapine, RMI-81582, and tiospirone revealed higher ratios of occupancy at 5-HT_2 versus D_2 receptors than haloperidol and pimozide in the present in vivo receptor binding method (Figures 3, 5, 6, 7; Table 1). The result supports previous reports by Meltzer et al. (1989a, b) suggesting that a series of atypical antipsychotics demonstrate relatively higher ratios of pKi values for 5-HT_2 receptors to those for D_2 receptors than typical antipsychotics in vitro. Moreover, the present result seems to fit the in vivo D_2 and 5-HT_2 receptor occupation profiles of several typical and atypical antipsychotic drugs that were recently assessed by Stockmeier et al. (1993) using [^{3}H]-N-methyl-spiperone as a ligand. This is supported by the finding that our results yielded a strong correlation with those of Stockmeier et al. (1993) regarding the pED_{50} values for D_2 receptor occupancy and the ratios of potency for 5-HT_2 versus D_2 receptor occupancy by the six test drugs. The reason for the lack of a correlation of the pED_{50} values for 5-HT_2 receptor occupation between the two studies is not readily apparent. It might be ascribed partly to the binding of [^{3}H]-N-methyl-spiperone to the cortical D_2 sites in the previous study, the binding of [^{3}H]-ketanserin to α_1-adrenoceptors or tetrabenazine sites (Roth et al. 1987) in our study, and/or some other factors.

There is a slight difference between clozapine and RMI-81582 with regard to 5-HT_2/D_2 ratio of receptor occupancy (Table 2; the difference of pED_{50} values, 2.53 RMI-81582 versus 1.63 for clozapine). In view of the fact that RMI-81582 has the same level of 5-HT_2/D_2 ratio of affinity with clozapine in vitro (Meltzer et al. 1989a) and in vivo (Stockmeier et al. 1993), this discrepancy is probably a result of the limited ability of both drugs to displace [^{3}H]-YM-09151-2 from D_2 receptors (Figures 5 and 6; Table 1). In fact, [^{3}H]-YM-09151-2 has a higher affinity for D_2 receptors than [^{3}H]-spiperone (Terai et al. 1989).

Chlorpromazine acts differently from other typical antipsychotics in that we found a four- to fivefold greater potency in occupying 5-HT_2 than D_2 receptors, which is comparable to the atypical antipsychotic tiospi-

rone (Figures 4 and 7; Table 1). The considerable degree of in vivo 5-HT_2 receptor occupation by chlorpromazine was recently reported (Matsubara et al. 1992; Stockmeier et al. 1993). The latter study also showed relatively low selectivity of tiospirone for 5-HT_2 versus D_2 receptors in vivo (only fourfold) as compared to that in vitro (25-fold, by Meltzer et al. 1989a). This kind of discrepancy seems to indicate the importance of measuring affinities for receptors of drugs in vivo, which enables estimation of potency of drugs including reference to their bioavailability (Stockmeier et al. 1993). Nash et al. (1988) reported that clozapine and some other atypical antipsychotics, but not chlorpromazine, block MK-212 (a 5-HT_2 agonist)-induced hyperthermia and corticosterone secretion in the rat. Also, it should be noted that clozapine and other atypical antipsychotics bind to other subtypes of 5-HT receptors with high affinity such as 5-HT_{1C} receptors (Roth et al. 1992) in addition to the 5-HT_2 sites. Thus, some other aspects of serotonin receptor antagonism together with the affinity for 5-HT_2 receptors would help further explain the mode of action of atypical antipsychotic drugs that have less ability to cause EPS than chlorpromazine.

The possible relevance of serotonin and serotonin-dopamine interaction in the pathophysiology of schizophrenia, as well as the role of antagonism of 5-HT_2 receptors in the mode of action of atypical antipsychotic drugs such as clozapine and risperidone, have been discussed extensively (Meltzer 1991; Kahn and Davidson 1993; Leysen et al. 1993; Meltzer et al. 1993; Stockmeier et al. 1993). The hypothesis is supported by the clinical observation that ritanserin, a strong 5-HT_2 receptor antagonist, ameliorates neuroleptic-induced extrapyramidal signs (Bersani et al. 1986) and that 5-HT_2 receptor antagonists are effective for negative symptoms of schizophrenia (Gelders 1989; Wiesel et al. 1994). Our current data revealing relatively high 5-HT_2 versus D_2 receptor occupancy by the tested atypical antipsychotics in vivo extended and are in line with the above discussion.

With regard to the classification of antipsychotics, we applied the criterion by Deutch et al. (1991) in which tiospirone as well as clozapine and RMI-81582 is classified as atypical. As to zotepine, some authors classified it as atypical (Meltzer et al. 1989a; Stockmeier et al. 1993) and others did not (Matsubara et al. 1992). We have included this drug in the third group, together with two iminodibenzyls mosapramine and clocapramine. It should be noted that the present study tried, for the first time, to investigate in vivo D_2 and 5-HT_2 receptor occupancy by the two iminodibenzyls. With the exceptions of chlorpromazine and tiospirone as discussed above, zotepine, mosapramine, and clocapramine fall somewhere between typical and atypical group with regard to a ratio of potency in occupying 5-HT_2 versus D_2 receptors (Table 1). Some clinical studies suggested zotepine is effective for psychiatric symptoms with less chance to cause extrapyramidal side effects than haloperidol (Fleischhacker et al. 1989; Barnas et al. 1992). In addition, it was reported that a low dose of zotepine is more efficacious in treating the negative symptoms in comparison with haloperidol (Barnas et al. 1992). Also, clinical trials revealed that two iminodibenzyl derivatives, mosapramine and clocapramine, have favorable clinical effects on negative symptoms in addition to some positive symptoms of schizophrenia (Kurihara et al. 1983; Yamagami et al. 1988; Asano et al. 1992). Indeed, clocapramine was shown to be superior to the atypical antipsychotic sulpiride in relieving negative symptoms as well as the hallucinations and delusions of chronic schizophrenic patients (Yamagami et al. 1988). If these clinical data are combined with the observation on the ratio of potency in occupying 5-HT_2 versus D_2 receptors of these drugs (Table 1), we can possibly say that mosapramine and clocapramine as well as zotepine have a certain degree of atypicality.

In conclusion, the current in vivo binding study measuring a receptor occupancy with selective ligands obtained results, which support the finding that atypical antipsychotic drugs generally possess a high affinity for 5-HT_2 receptors with a relatively low affinity for D_2 receptors. Moreover, some iminodibenzyls were shown to have a certain degree of pharmacological characteristic of atypical antipsychotic drugs by these criteria.

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REFERENCES

Asano Y, Ito K, Onodera I, Ito K, Narita H (1992): Study of long-term administration of Y-156 in schizophrenia. 18th Collegium-Internationale Neuro-Psychopharmacologicum P-17-19

Barnas C, Stuppack CH, Miller C, Haring C, Sperner-Uterweger B, Fleischhacker WW (1992): Zotepine in the treatment of schizophrenic patients with prevailingly negative symptoms: A double-blind trial vs. haloperidol. Int Clin Psychopharmacol 7:23–27

Bersani G, Grispini A, Marini S, Pasini A, Valducci M, Ciani A (1986): Neuroleptic-induced extrapyamidal side effect: Clinical perspectives with ritanserin (R 55667), a new selective 5-HT_2 receptor blocking agent. Curr Ther Res 40:492–499

Bischoff S (1992): Limbic selective neuroleptics. 18th Congress

of Collegium-Internationale Neuro-Psychopharmacologicum S-56-178

Creese I, Burt DR, Snyder SH (1976): Dopamine receptor binding predicts clinical and pharmacological potencies of anticholinergic drugs. Science 192:481–483

Deutch AY, Moghaddam B, Innis RB, Krystal JH, Aghajanian GK, Bunney BS, Charney DS (1991): Mechanism of action of atypical antipsychotic drugs: Implication for novel therapeutic strategies for schizophrenia. Schizophr Res 4:121–156

Fleischhacker WW, Barnas C, Stuppack CH, Unterweger B, Miller C, Hinterhuber H (1989): Zotepine vs. haloperidol in paranoid schizophrenia: A double-blind trial. Psychopharmacol Bull 25:97–100

Gelders YG (1989): Thymosthenic agent, a novel approach in the treatment of schizophrenia. Schizophr Res 4: 121–156

Goeders NE, Kuhar MJ (1985): Benzodiazepine receptors binding in vivo with [^{3}H]-Ro 15-1788. Life Sci 37:345–355

Hatano K, Ishikawa K, Kawasaki K, Hatazawa J, Ito M, Ido T (1989): D_2-dopamine receptor specific brain uptake of carbon-11-labeled YM-09151-2. J Nucl Med 30:515–522

Kahn RS, Davidson M (1993): Serotonin, dopamine and their interactions in schizophrenia: an editorial. Psychopharmacology 112:S40–S54

Kane JM, Honigfeld G, Singer J, Meltzer HY, the Crozaril Collaborative Study Group (1988): Clozapine for the treatment-resistant schizophrenics: A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796

Kurihara M, Ito S, Kato N, Kawakita S, Kudo Y, Mori O (1983): Clinical evaluation of clocapramine (Clofekton^R) in schizophrenia: A double blind comparison of clocapramine, haloperidol and perphenazine. Clin Psychiat 12:519–538 (in Japanese)

Laduron PM, Janssen PFM, Leysen JE (1982): In vivo binding of [^{3}H]-ketanserin on serotonin S_2 receptors in rat brain. Eur J Pharmacol 81:43–48

Leysen JE, Janssen PMF, Gommeren W, Wynants J, Pauwels PJ, Janssen PAJ (1992): In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotics risperidone and ocaperidone. Mol Pharmacol 41:494–508

Leysen JE, Janssen PMS, Schotte A, Luyten WHML, Megens AAHP (1993): Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: Role of $5HT_2$ receptors. Psychopharmacology 112:S40–S54

Matsubara S, Matsubara R, Kusumi I, Koyama T, Yamashita I (1992): Dopamine D_1, D_2 and serotonin$_2$ receptor occupation by typical and atypical antipsychotic drugs *in vivo*. J Pharmacol Exp Ther 265:498–508

Meltzer HY, Matsubara S, Lee JC (1989a): Classification of typical and atypical antipsychotic drugs on the basis of dopamine D_1, D_2 and serotonin$_2$ pKi values. J Pharmacol Exp Ther 251:238–246

Meltzer HY, Matsubara S, Lee JC (1989b): The ratios of serotinin$_2$ and dopamine$_2$ affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull 25:390–392

Meltzer HY (1991): The neurobiology of schizophrenia. Curr Opin Psychiat 4:90–95

Meltzer HY, Maes M, Lee MA (1993): The cimetidine-induced increase in prolactin secretion in schizophrenia: Effect of clozapine. Psychopharmacology 112:S95–S104

Miller LG, Greenblatt DJ, Paul SM, Shader RI (1987): Benzodiazepine occupancy in vivo: Correlation with brain concentrations and pharmacodynamic action. J Pharmacol Exp Ther 240:516–522

Moore NC, Gershon S (1989): Which atypical antipsychotics are identified by screening tests? Clin Neuropharmacol 12:167–184

Nash JF, Meltzer HY, Gudelsky GA (1988): Antagonism of serotonin receptor mediated neuroendocrine and temperature responses by atypical neuroleptics in the rat. Eur J Pharmacol 151:463–469

Neale R, Gerhardt S, Liebmann JM (1983): Effect of the novel antipsychotics, RMI-81582 and clozapine, on predictions of extrapyramidal liability in squirrel monkeys. Drug Dev Res 3:171–176

Niznik HB, Grigoriadis DE, Pri-Bar I, Buchman O, Seeman P (1985): Dopamine D_2 receptor selectivity labeled by a benzamide neuroleptic: [^{3}H]-YM-09151-2. Naunyn-Schmiedelberg's Arch Pharmacol 329:333–343

Nordström AL, Farde L, Halldin C (1993): High 5-HT_2 receptor occupancy in clozapine treated patients demonstrated by PET. Psychopharmacology 110:365–367

Nyberg S, Farde L, Eriksson L, Halldin C, Eriksson B (1993): 5-HT_2 and D_2 dopamine receptor occupancy in the living human brain: A PET study with risperidone. Psychopharmacology 110:265–272

Paalzow LK, Edlund PO (1979): Multiple receptor responses: A new concept to describe the relationship between pharmacological effects and pharmacokinetics of a drug: Studies on clonidine in the rat and cat. J Pharmacokin Biopharm 7:495–510

Porsolt RD, Jafre M (1981): Neuroleptic-induced acute dyskinesias in rhesus monkeys. Psychopharmacology 75: 16–21

Roth BL, McLean S, Zhu XZ, Chuang DM (1987): Characterization of two [^{3}H]ketanserin recognition sites in rat striatum. J Neurochem 49:1833–1838

Roth BL, Ciaranello RD, Meltzer HY (1992): Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT_{1C} receptors. J Pharmacol Exp Ther 260: 1361–1365

Seeman P, Lee T, Chau-Wong M, Wong K (1976): Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261:717–718

Sovner R, DiMascio A (1978): Extrapyramidal syndromes and other neurological side effects of psychotropic drugs. In Lipton MA, DiMascio A, Kilam KF (eds), Psychopharmacology: A Generation of Progress. New York, Raven Press, pp 1021–1032

Stockmeier CA, DiCarlo JJ, Zhang Y, Thompson P, Meltzer HY (1993): Characterization of typical and atypical antipsychotic drugs based on in vivo occupation of serotonin$_2$ and dopamine$_2$ receptors. J Pharmacol Exp Ther 266: 1374–1384

Sumiyoshi T, Kido H, Sakamoto H, Urasaki K, Suzuki K,

Yamaguchi N, Mori H, Shiba K, Yokogawa K, Ichimura F (1993): Time course of dopamine-D_2 and serotonin-$5HT_2$ receptor occupancy rates by haloperidol and clozapine in vivo. Jpn J Psychiatr Neurol 47:131–137

Sumiyoshi T, Kido H, Sakamoto H, Urasaki K, Suzuki K, Yamaguchi N, Mori H, Shiba K, Yokogawa K (1994a): In vivo dopamine-D_2 and serotonin-5-HT_2 receptor binding study of risperidone and haloperidol. Pharmacol Biochem Behav 47:553–557

Sumiyoshi T, Kido H, Sakamoto H, Urasaki K, Suzuki K, Yamaguchi N, Mori H, Shiba K (1994b): Time course of dopamine$_{1,2}$ and serotonini$_2$ receptor binding of antipsychotics in vivo. Pharmacol Biochem Behav 49:165–169

Terai M, Hidaka K, Nakamura Y (1989): Comparison of [^{3}H]YM-09151-2 with [^{3}H]spiperone and [^{3}H]raclopride for dopamine D-2 receptor binding to rat striatum. Eur J Pharmacol 173:177–182

Wiesel FA, Nordstrom AL, Farde L, Eriksson B (1994): An open clinical and biochemical study of ritanserin in acute patients with schizophrenia. Psychopharmacology 114: 31–38

Yamagami S, Kiriike N, Kawaguchi K (1988): A single-blind study of clocapramine and sulpiride in hospitalized chronic schizophrenic patients. Drugs Exptl Clin Res 14:707–713

Young MA, Meltzer HY (1980): RMI-81,582, a novel antipsychotic drug. Psychopharmacology 67:101–106