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In Vivo Dopamine-D_2 and Serotonin-5-HT_2 Receptor Binding Study of Risperidone and Haloperidol

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SUMIYOSHI, T., H. KIDO, H. SAKAMOTO, K. URASAKI, K. SUZUKI, N. YAMAGUCHI, H. MORI, K. SHIBA AND K. YOKOGAWA. *In vivo dopamine-D_2 and serotonin-5-HT_2 receptor binding study of risperidone and haloperidol.* PHARMACOL BIOCHEM BEHAV 47(3) 553-557, 1994.—An in vivo receptor binding technique was applied to evaluate the affinities of risperidone and haloperidol for dopamine-D_2 receptors (D_2) and serotonin-5-HT_2 receptors (5-HT_2) in rat brain with [^{3}H]YM-09151-2 and [^{3}H]ketanserin as selective ligands. Radioactivities were obtained in the striatum, frontal cortex, and cerebellum of the rats treated with the ligands. Time course study of receptor occupancy at 25 to 250 min after single doses of the drugs (1 mg/kg, IP) showed higher 5-HT_2 occupancy in the frontal cortex and lower D_2 occupancy in the striatum by risperidone than by haloperidol. Dose-response analysis of receptor occupancy revealed risperidone demonstrated higher binding affinity for 5-HT_2 than for D_2, while the reverse was observed with haloperidol. It appeared that risperidone (1 mg/kg, IP), but not haloperidol (1 mg/kg, IP), demonstrated regional selectivity in D_2 occupancy favouring frontal cortex more than the striatum. That risperidone displayed a higher ratio of 5-HT_2 to D_2 in occupancy than haloperidol is in agreement with the previous findings obtained in vitro.

Risperidone D_2 receptor 5-HT_2 receptor In vivo receptor binding Time course study Dose-response analysis Haloperidol

RISPERIDONE (R 64 766, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pyperidinyl]ethyl}-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one) is a recently developed antipsychotic drug. Several clinical studies, including international multicenter trials (4,8,16,18,26), have reported efficacy of the drug in the treatment of schizophrenia. Clinical studies suggest that risperidone, when compared with traditional antipsychotics such as haloperidol, is more efficacious in treating the negative symptoms of schizophrenia and less likely to produce disturbances of the extrapyramidal motor system (8,16,26). Considerable attention has been paid to the role of antagonism of 5-HT_2 receptors in schizophrenia due to the fact that addition of ritanserin, a potent and specific 5-HT_2 antagonist, to treatment with antipsychotics such as haloperidol reduced extrapyramidal symptoms (1), and that clozapine, a prototype of atypical antipsychotic drugs with relatively strong affinity for 5-HT_2 (19), has demonstrated favourable clinical efficacy for both positive and negative symptoms of patients who were resistant to treatment with traditional antipsychotics (11). Risperidone also was shown to possess a very high binding affinity for 5-HT_2 (K_i = 0.16 nM; for haloperidol, K_i = 25.1 nM) with a relatively high affinity for dopamine D_2 receptors (K_i = 3.13 nM; for haloperidol, K_i = 1.55 nM) (3,14) in receptor binding studies. The receptor dissociation half-lives of risperidone for 5-HT_2 and D_2 are 31 and 2.7 min, respectively (6.6 and 5.8 min for haloperidol) (14). These properties may explain clinical utility of the drug (10,14,15).

The majority of these receptor binding studies, however, were performed under in vitro conditions and only a few studies (2,15) have investigated whether risperidone reveals similar

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degrees of blockade of the receptors under in vivo conditions. Discrepancies in drug effects on the dopamine receptor binding between in vitro and in vivo were indicated (23).

The present study was designed to evaluate the in vivo binding affinities of risperidone for 5-HT_2 and D_2 receptors in rat brain tissue with haloperidol as a reference compound using selective radioactive ligands. Radioactive derivatives of YM-09151-2 and ketanserin have formerly been shown to bind selectively in vivo to D_2 and 5-HT_2 receptors, respectively (7,13). An in vivo binding technique was applied where [^{3}H]YM-09151-2 and [^{3}H]ketanserin were IV administered while the subjects were alive and the occupancy of the receptors by the drugs was measured. The time courses for D_2 and 5-HT_2 occupancy in the frontal cortex and D_2 occupancy in the striatum were followed and the dose-response relation of D_2 and 5-HT_2 occupancy by risperidone and haloperidol was analyzed.

METHOD

[^{3}H]YM-09151-2 (specific activity 3.22 TBq/mmol) and [^{3}H]ketanserin (specific activity 2.22 TBq/mmol) were purchased from New England Nuclear Corporation. Haloperidol was obtained as a gift from Dainippon Pharmaceutical Ltd. (Japan) and risperidone was a gift from Janssen Research Foundation (Belgium).

For the kinetic study, male Wistar rats (220–240 g) were treated IP with haloperidol 1 mg/kg, risperidone 1 mg/kg, or the same volume of the corresponding vehicle (dimethyl sulfoxide), 10 min before the ligand injection. The ligands ([^{3}H]YM-09151-2 for D_2 receptors or [^{3}H]ketanserin for 5-HT_2 receptors) were injected IV into the lateral tail vein (1540–1680 kBq/kg body weight). The rats were sacrificed by decapitation at 15, 30, 45, 60, 120, or 240 min after injections of ligands. 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 (Packard Soluene 350) by incubation for 2–3 h at 50°C. A scintillation cocktail (New England Nuclear Aquasol 2) was added to the solubilized tissues adjusted to pH 7.0 with 0.5 N HCl solution (for inhibition of pseudofluorescence). After 12 to 24 h, the radioactivity concentrations in the tissues were counted with a liquid scintillation counter (Aloka LSC-1000) and the values, expressed as % dose/g tissue, were calculated. Receptor occupancy was determined by a modification of the method of previous reports (5,20): 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.

Statistical Analysis

Receptor occupancy by risperidone and haloperidol was compared by means of two-way ANOVAs followed by Tukey's multiple comparisons of the means.

To evaluate the dose dependency of D_2 and 5-HT_2 receptor occupancy assessed with the present method, male Wistar rats were injected IP with 0.1, 0.5, 1.0, 2.0, 5.0, or 10 mg/kg of haloperidol, risperidone, or the same volume of a control vehicle (dimethyl sulfoxide). Ten minutes later, [^{3}H]YM-09151-2 or [^{3}H]ketanserin (1540–1680 kBq/kg body weight) was administered IV into the tail vein. Sixty minutes after the ligand injections, the animals were sacrificed and the brains were rapidly removed and dissected to obtain cerebellum, striatum, frontal cortex, and the rest of the brain. The rest of the procedure to obtain D_2 and 5-HT_2 receptor occupancy by haloperidol and risperidone was the same as described above. The dose–response curves were analyzed with the minimal-square method (21).

TABLE 1

THE AMOUNT OF RADIOACTIVITY DETECTED IN EACH BRAIN REGION OF THE VEHICLE-TREATED RATS TREATED WITH [^{3}H]YM-09151-2

Region	Time After Ligand Injection (min)	Radioactivity (% dose/g tissue)
Frontal cortex	15	0.758 ± 0.061
	30	0.789 ± 0.066
	45	0.741 ± 0.113
	60	0.654 ± 0.051
	120	0.539 ± 0.068
	240	0.479 ± 0.040
Striatum	15	1.296 ± 0.134
	30	1.713 ± 0.122
	45	1.836 ± 0.339
	60	1.695 ± 0.151
	120	1.853 ± 0.180
	240	1.947 ± 0.267
Cerebellum	15	0.648 ± 0.037
	30	0.656 ± 0.058
	45	0.644 ± 0.069
	60	0.552 ± 0.066
	120	0.478 ± 0.027
	240	0.375 ± 0.022

Values of radioactivity are mean ± SD of five rats per group.

RESULTS

The values of radioactivity in each brain region at the different time intervals after the injection of [^{3}H]YM-09151-2

TABLE 2

THE AMOUNT OF RADIOACTIVITY DETECTED IN EACH BRAIN REGION OF THE VEHICLE-TREATED RATS TREATED WITH [^{3}H]KETANSERIN

Region	Time After Ligand Injection (min)	Radioactivity (% dose/g tissue)
Frontal cortex	15	0.313 ± 0.060
	30	0.301 ± 0.070
	45	0.268 ± 0.033
	60	0.254 ± 0.034
	120	0.181 ± 0.029
	240	0.080 ± 0.010
Cerebellum	15	0.130 ± 0.020
	30	0.105 ± 0.023
	45	0.102 ± 0.019
	60	0.092 ± 0.013
	120	0.067 ± 0.011
	240	0.058 ± 0.006

Values of radioactivity are mean ± SD of five rats per group.

with vehicle-treated rats are shown in Table 1. The values were highest in the striatum followed by those in frontal cortex and cerebellum. As to [^{3}H]ketanserin-treated rats, the values in frontal cortex continued to be higher than those in cerebellum (Table 2). Using these values and the corresponding data with the drug-treated rats, the D_2 and 5-HT_2 receptor occupancies were calculated.

Time courses of D_2 receptor occupancy in the striatum by risperidone (1 mg/kg, IP) and haloperidol (1 mg/kg, IP) are shown in Fig. 1. Haloperidol demonstrated significantly higher occupancy than risperidone, $F(1, 42) = 27.16$, $p < 0.01$. Among the various time points (15, 30, 45, 60, 120, 240 min after the ligand injection), no significant variations in the D_2 receptor occupancy were observed within either the risperidone- or haloperidol-treated groups. In contrast, 5-HT_2 receptor occupancy in the frontal cortex by risperidone was significantly higher than that by haloperidol, $F(1, 42) = 173.95$, $p < 0.01$, as shown in Fig. 2. Among the various time points (15, 30, 45, 60, 120, 240 min after the ligand injection), the 5-HT_2 receptor occupancy at 240 min was significantly lower than those at the rest of the time points in risperidone-treated groups ($p < 0.01$). In the haloperidol-treated groups, the receptor occupancy at 240 min was significantly lower than those at 30, 45, 60, and 120 min ($p < 0.01$).

Figure 3 and 4 show the occupancy of D_2 and 5-HT_2 receptors following various doses (0.1–10 mg/kg) of risperidone and haloperidol at 60 min after the ligand injections (70 min after drug administrations). This time point was chosen based on the stable D_2 and 5-HT_2 receptor occupancy by both drugs at that time point, as observed in Figs. 1 and 2. The following relations between the occupancy Φ (%) and doses of the drugs (D mg/kg) were observed: $\Phi = \Phi_{max} \times D^S/(D^S + 1/Q)$ (Q, S are constants, defined for the Hill equation to relate the occupancy to the dose of the drug) (21). For risperidone, $\Phi_{max} = 100$, $S = 0.72 \pm 0.16$, $Q = 2.13 \pm 0.61$ (for D_2), $\Phi_{max} = 98.3 \pm 1.1$, $S = 0.95 \pm 0.36$, $Q = 58.8 \pm 51.8$ (for 5-HT_2), and for haloperidol, $\Phi_{max} = 100$, $S = 0.99 \pm 0.37$, $Q = 0.74 \pm 0.35$ (for D_2), $\Phi_{max} = 77.2 \pm 4.6$, $S = 1.29 \pm 0.06$, $Q = 0.90 \pm 0.14$ (for 5-HT_2) (mean ± SD).

Figure 5 shows the time course of D_2 receptor occupancy in the frontal cortex for haloperidol (1 mg/kg, IP) and risperidone (1 mg/kg, IP). In this region, no significant difference between the occupancy by the drugs was observed.

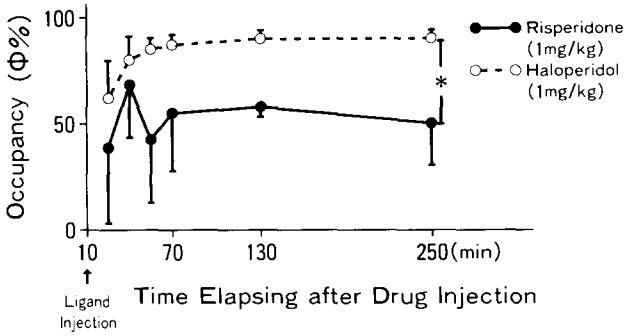

FIG. 1. Time course of D_2 receptor occupancy (Φ%) in rat striatum after single doses (1 mg/kg, IP) of risperidone and haloperidol. [^{3}H]YM-09151-2 (1540–1680 kBq/kg body weight) was injected into a tail vein 10 min after drug administration. Each point represents the mean ± SD (n = 4–5). $\Phi = [1 - (X_D - X_{nD})/(X_S - X_{nS})] \times 100$ (%), where each abbreviation represents radioactivity (% dose/g tissue) of X_D, striatum of drug-treatd rat; X_{nD}, cerebellum of drug-treated rat; X_S, striatum of vehicle-treated rat; X_{nS} cerebellum of vehicle-treated rat. *$p < 0.01$. Comparison by two-way ANOVAs followed by Tukey's multiple comparisons of the means. (Ordinate, occupancy for D_2 receptors; abscissa, time after the injection of risperidone or haloperidol.)

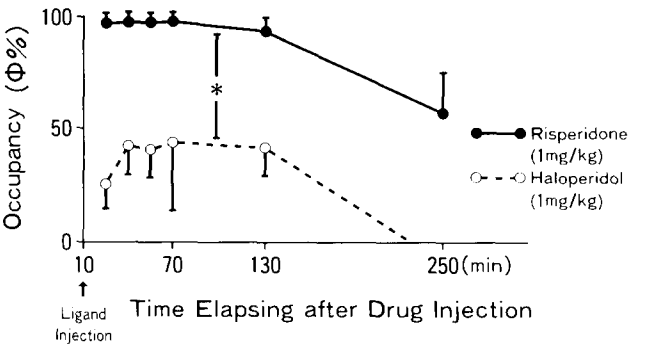

FIG. 2. Time course of 5-HT_2 receptor occupancy (Φ%) in rat frontal cortex after single doses (1 mg/kg, IP) of risperidone and haloperidol. [^{3}H]Ketanserin (1540–1680 kBq/kg body weight) was injected into a tail vein 10 min after drug administration. Each point represents the mean ± SD (n = 3–5). $\Phi = [1 - (X_D - X_{nD})/(X_S - X_{nS})] \times 100$ (%), where each abbreviation represents radioactivity (% dose/g tissue) of X_D, frontal cortex of drug-treated rat X_{nD}, cerebellum of drug-treated rat; X_S, frontal cortex of vehicle-treated rat; X_{nS}, cerebellum of vehicle-treated rat. *$p < 0.01$. Comparison by two-way ANOVAs followed by Tukey's multiple comparisons of the means. (Ordinate, occupancy for 5-HT_2 receptors; abscissa, time after the injection of risperidone or haloperidol.)

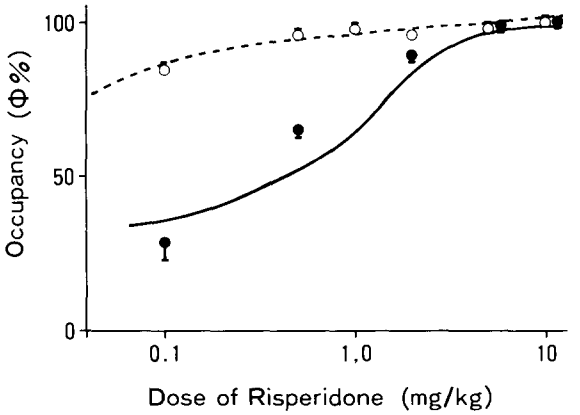

FIG. 3. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of risperidone. [^{3}H]YM-09151-2 or [^{3}H]ketanserin (1540–1680 kBq/kg body weight) was injected into a tail vein 10 min after administration (IP) with 0.1, 0.5, 1.0, 2.0, 5.0, or 10 mg/kg of risperidone. Sixty minutes after the ligand injection, radioactivity in the striatum, frontal cortex, and cerebellum was counted. Each point represents the mean ± SE (n = 4–5). $\Phi = [1 - (X_D - X_{nD})/(X_S - X_{nS})] \times 100$ (%), 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 receptors; ○, 5-HT_2 receptors. (Ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of risperidone.)

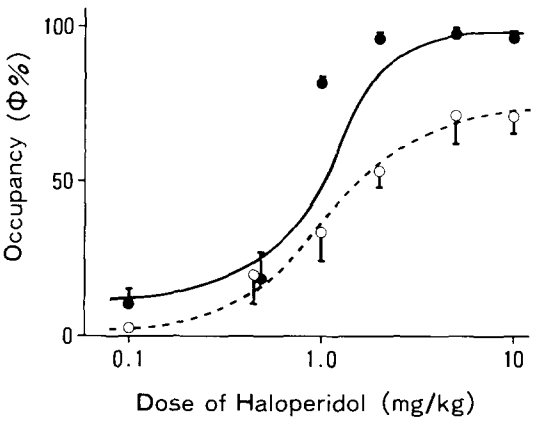

FIG. 4. Occupancy (Φ%) of striatal D_2 and frontal 5-HT_2 receptors in rat brain with various doses of haloperidol. [^{3}H]YM-09151-2 or [^{3}H]ketanserin (1540–1680 kBq/kg body weight) was injected into a tail vein 10 min after administration (IP) with 0.1, 0.5, 1.0, 2.0, 5.0, or 10 mg/kg of haloperidol. Sixty minutes after the ligand injection, radioactivity in the striatum, frontal cortex and cerebellum was counted. Each point represents the mean ± SE (n = 4–5). $\Phi = [1 - (X_D - X_{nD})/(X_S - X_{nS})] \times 100$ (%), 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 receptors; ○, 5-HT_2 receptors. (Ordinate, occupancy for D_2 and 5-HT_2 receptors; abscissa, dose of haloperidol.)

The ratios of the D_2 receptor occupancy in the frontal cortex to those in the striatum by the drugs at every time point were calculated for each individual rat tested. Statistical analysis by means of two-way ANOVAs revealed that the mean of the frontal D_2/striatal D_2 ratios of occupancy of the risperidone-treated groups (1.78) (n = 24) was significantly higher than that of the haloperidol-treated groups (1.03) (n = 26), $F(1, 38) = 9.14, p < 0.01$.

DISCUSSION

A limited number of studies have revealed the in vivo binding profiles of several classes of antipsychotic drugs to 5-HT_2 and D_2 receptors (2,15,22). The ratio of potency of antipsychotics in displacing 5-HT_2 and D_2 receptor binding in vivo was reported to discriminate between typical and atypical antipsychotics (22). Risperidone also has been shown to have a higher binding affinity for 5-HT_2 and a lower affinity for D_2 than haloperidol both in vitro (14) and in vivo (15).

The present trial differs from these former studies in that selective radioactive ligands for the respective receptors were applied. Moreover, radioactivities at various time points during in vivo competition for receptor occupancy between the radioligand and the drugs were measured in this study. This observation seems important because the binding of a ligand to receptors does not reach an equilibrium in vivo.

Under the present experimental conditions, radioactivities were counted in the striatum, frontal cortex, and cerebellum of the [^{3}H]YM-09151-2-treated rats, and in the frontal cortex and cerebellum of the [^{3}H]ketanserin-treated rats, with the lowest radioactivities in the cerebellum (Tables 1 and 2).

Risperidone at an IP dose of 1 mg/kg revealed higher 5-HT_2 and lower D_2 receptor occupancy than haloperidol 1 mg/kg by the in vivo time course study (Figs. 1 and 2). In this regard, we have recently shown that clozapine 20 mg/kg maintains higher 5-HT_2 and lower D_2 receptor occupancy in comparison with haloperidol 1 mg/kg and 10 mg/kg under the same experimental conditions (24,25). The predominant degree of 5-HT_2 blockade by risperidone was further supported by the finding in the dose-response analysis of the receptor occupancy (Figs. 3 and 4). Receptor occupancies counted at 60 min after the ligand injection were adopted as constituents of these dose-response curves based on the stabilized occupancy of striatal D_2 and frontal 5-HT_2 at this time point, as observed in Figs. 1 and 2. A large standard deviation of the constants in the formula for 5-HT_2 occupancy by risperidone was due to a lack of data at doses lower than 0.1 mg/kg. Risperidone demonstrated higher binding affinity for 5-HT_2 than for D_2 (Fig. 3), and the reverse was observed with haloperidol (Fig. 4). These results seem to correspond well with a previous report assessing in vivo occupancy by risperidone and haloperidol, in which [^{3}H]spiperone, a ligand with lower selectivity than the currently used ones, was applied (15). The relatively high dose of haloperidol to occupy 50% of striatal D_2 receptors was observed (Fig. 4, 1 mg/kg) compared to 0.16 mg/kg in the previous study (15). The difference in the route of drug injection (IP vs. SC) or the higher affinity of [^{3}H]YM-09151-2 for D_2 receptors than [^{3}H]spiperone (27) may account for this discrepancy.

It was also implied that risperidone 1 mg/kg IP has a preference for the frontal cortex over the striatum regarding D_2 occupancy in vivo, compared with the same dose of haloperidol (Figs. 1 and 5). A recent study has described chronic administration of haloperidol and an atypical antipsychotic clozapine caused a significant increase in D_2 density in frontal cortex, but only haloperidol caused a significant increase in D_2 density in the striatum, suggesting clozapine exerts a regionally specific effect on D_2 receptors (9). Another neurophysiological study demonstrated clozapine acutely increases the firing rate of A10 dopamine cells projecting to the frontal cortex but not A9 dopamine cells projecting to the striatum,

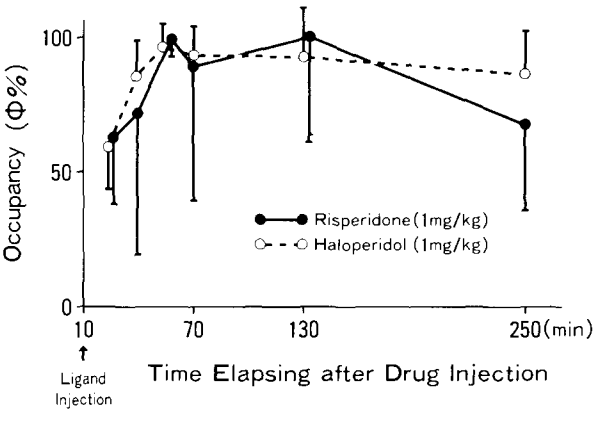

FIG. 5. Time course of D_2 receptor occupancy (Φ%) in rat frontal cortex after single doses (1 mg/kg, IP) of risperidone and haloperidol. [^{3}H]YM-09151-2 (1540–1680 kBq/kg body weight) was injected into a tail vein 10 min after drug administration. Each point represents the mean ± SD (n = 4–5). $\Phi = [1 - (X_D - X_{nD})/(X_S - X_{nS})] \times 100$ (%), where each abbreviation represents radioactivity (% dose/g tissue) of X_D, frontal cortex of drug-treated rat; X_{nD}, cerebellum of drug-treated rat; X_S, frontal cortex of vehicle-treated rat; X_{nS}, cerebellum of vehicle-treated rat. (Ordinate, occupancy for D_2 receptors; abscissa, time after the injection of risperidone or haloperidol.)

and haloperidol increases the firing rate of both subpopulations of dopamine neurons (6). In view of the fact that risperidone shares with clozapine some favourable clinical effects of atypical antipsychotics, the regional selectivity in D_2 occupancy demonstrated in the current study may explain some pharmacological properties of risperidone. Labelling of D_2 receptors in rat frontal cortex was demonstrated with [^{3}H]YM-09151-2 as a ligand in vitro (12). But it was also reported that the density of D_2 receptors in the frontal cortex is about 4% of their density in the striatum (17). Therefore, the receptors labelled by [^{3}H]YM-09151-2 in the frontal cortex under the current in vivo condition should be carefully characterized. To clarify further the selectivity of risperidone favouring frontal D_2 receptors, investigation of occupancy of frontal D_2 receptors with various doses of risperidone may be desirable.

In conclusion, it was confirmed by the present in vivo receptor binding technique, applying selective ligands, that risperidone has a higher affinity for 5-HT_2 receptors in comparison with haloperidol. There appears a possibility that risperidone may possess regional selectivity in D_2 occupancy (frontal cortex > striatum), which requires further study.

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