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Time Course of Dopamine_{1,2} and Serotonin₂ Receptor Binding of Antipsychotics In Vivo

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SUMIYOSHI, T., H. KIDO, H. SAKAMOTO, K. URASAKI, K. SUZUKI, N. YAMAGUCHI, H. MORI AND K. SHIBA. *Time course of dopamine_{1,2} and serotonin₂ receptor binding of antipsychotics in vivo*. PHARMACOL BIOCHEM BEHAV 49(1) 165-169, 1994.—An in vivo receptor binding technique was applied to evaluate the affinities of clozapine (20 mg/kg), RMI-81582 (20 mg/kg), and haloperidol (1 mg/kg) for dopamine D₁, D₂ and serotonin 5-HT₂ receptors in rat brain with [³H]-SCH23390, [³H]-YM-09151-2, and [³H]-ketanserin as selective ligands. The time course study of receptor occupancy at 25 to 250 min after intraperitoneal administration of the drugs showed higher 5-HT₂ and lower D₂ receptor occupancies of clozapine and RMI-81582 than those of haloperidol both in the striatum and frontal cortex. The 5-HT₂/D₂ ratios of receptor occupancy for clozapine and RMI-81582 were about 6 to 8 times higher than that for haloperidol. Stable occupancies of D₁ receptors were observed only with RMI-81582 and clozapine, the former demonstrating the higher occupancy. These findings are in agreement with the previous findings obtained under in vitro conditions and may account for some part of the properties of atypical antipsychotic drugs.

In vivo receptor binding D₁, D₂, 5-HT₂ receptors Clozapine RMI-81582 Time course study

RECENT researches have concentrated on the development of antipsychotic drugs that are not accompanied by extrapyramidal symptoms (EPS) and have negative symptoms relieving efficacy. One of the clues is the concept of atypical antipsychotic drugs (AAPDs), defined as those that do not cause EPS, elevation of serum prolactin, or catalepsy in rats (17). Attempts have been made to characterize the pharmacology of AAPDs. High affinity for dopamine D₁ receptors (D₁) (30), higher serotonin 5-HT₂ receptors (5-HT₂)/dopamine D₂ receptors (D₂) ratios of pKi values (18), or some other peculiarities were indicated. The majority of these kinds of receptor binding studies was performed under in vitro conditions. However, because of the discrepancies between the in vitro and in vivo findings about the blocking effects on D₁, D₂ (2,25) and 5-HT₂ (20) receptors, more precise in vivo studies on receptor binding features of AAPDs are necessary.

Clozapine, a prototype of AAPDs, and its structurally related compound RMI-81582 were reported to exert their effects without causing EPS or elevation of serum prolactin levels in patients (31) and in laboratory animals (21,23).

Herein, the receptor binding properties of these AAPDs

were examined in comparison with a typical antipsychotic drug under in vivo conditions. Selective radioactive ligands for D₁, D₂, and 5-HT₂ receptors were intravenously injected into rats after administration of clozapine, RMI-81582, or haloperidol to follow the time course of the occupancy of the receptors in the brain by the drugs.

METHOD

[³H]-SCH23390 (specific activity 2.78 TBq/mmol), [³H]-YM-09151-2 (specific activity 3.22 TBq/mmol), and [³H]-ketanserin (specific activity 2.22 TBq/mmol) were purchased from New England Nuclear Corporation. Haloperidol, clozapine, and RMI-81582 were obtained as gifts from Dainippon Pharmaceutical Ltd. (Japan), Sandoz Pharmaceutical Ltd. (Switzerland), and Marion Merrill Dow Research Institute (USA), respectively.

Male Wistar rats (220-240 g) were treated intraperitoneally with haloperidol 1 mg/kg, clozapine 20 mg/kg, RMI-81582 20 mg/kg, or the same volume of the corresponding vehicle (dimethyl sulfoxide), 10 min before the ligand injection. The

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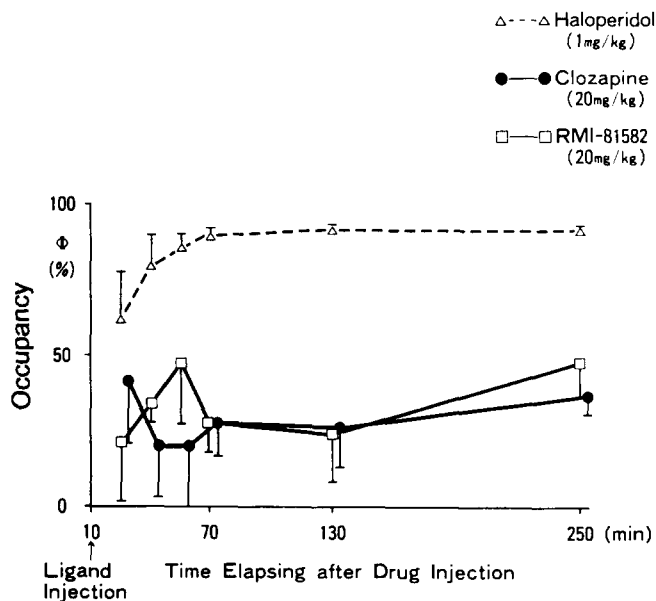


FIG. 1. Time course of D_2 receptor occupancy ($\Phi\%$) in rat striatum after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [^3H]-YM-09151-2 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean \pm 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 , striatum of drug-treated rat; X_{nD} , cerebellum of drug-treated rat; X_S , striatum of vehicle-treated rat; X_{nS} , cerebellum of vehicle-treated rat.

RESULTS

Time courses of D_2 receptor occupancy in the striatum by haloperidol (1 mg/kg IP), clozapine (20 mg/kg IP), and RMI-81582 (20 mg/kg IP) are shown in Fig. 1. Haloperidol demonstrated significantly higher occupancy than clozapine, $F(1, 38) = 193.73$, $p < 0.01$, and RMI-81582, $F(1, 41) = 201.83$, $p < 0.01$. In the frontal cortex also, haloperidol revealed higher D_2 receptor occupancy than clozapine, $F(1, 35) = 37.58$, $p < 0.01$, and RMI-81582, $F(1, 42) = 11.88$, $p < 0.01$ (Fig. 2). By contrast, 5-HT₂ receptor occupancy in the frontal cortex by clozapine, $F(1, 31) = 129.05$, $p < 0.01$, and RMI-81582, $F(1, 32) = 93.57$, $p < 0.01$, were significantly higher than those by haloperidol as described in Fig. 3 (comparisons made with data at 15–120 min after the injection of [^3H]-ketanserin). Clozapine, $F(1, 31) = 41.10$, $p < 0.01$, and RMI-81582, $F(1, 31) = 30.73$, $p < 0.01$, revealed higher 5-HT₂ receptor occupancy than haloperidol also in the striatum (comparisons with data at 15–120 min after the injection of [^3H]-ketanserin) (Fig. 4). Among the various time points (15, 30, 45, 60, 120, 240 min after the ligand injection), the 5-HT₂ receptor occupancy at 240 min were small and unstable in haloperidol treated groups in both of the regions (data points not shown in the figures). As for D_1 receptors, only RMI-81582 and clozapine showed stable occupancies in the striatum and frontal cortex, whereas the D_1 occupancies by haloperidol were small and unstable. RMI-81582 demonstrated significantly higher receptor occupancy than clozapine both in the striatum, $F(1, 41) = 240.19$, $p < 0.01$ (Fig. 5) and in the frontal cortex, $F(1, 38) = 91.51$, $p < 0.01$ (Fig. 6).

The results of these kinetic studies indicated that haloperi-

doses of the drugs were carefully chosen based on the in vitro affinities for D_2 and clinical dosage. The ligands [^3H]-SCH23390 for D_1 , [^3H]-YM-09151-2 for D_2 , or [^3H]-ketanserin for 5-HT₂ receptors were injected intravenously into the lateral tail vein (1.54–1.68 MBq/kg body weight). The rats were sacrificed by decapitation at 15, 30, 45, 60, 120, or 240 min after the injections of the 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 (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. The receptor occupancy ($\Phi\%$) were calculated as follows (11,19,27,28): $\Phi = [1 - (X_D - X_{nD}) / (X_S - X_{nS})] \times 100(\%)$, where each abbreviation represents the radioactivity 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 (if the radioactivity of X_D decreases as a result of the occupation of the specific region by the drugs, Φ value will approach 100%; the radioactivities in the cerebellum are supposed to represent the nonspecific binding).

Receptor occupancies were compared by means of two-way ANOVAs followed by Tukey's multiple comparisons of the means.

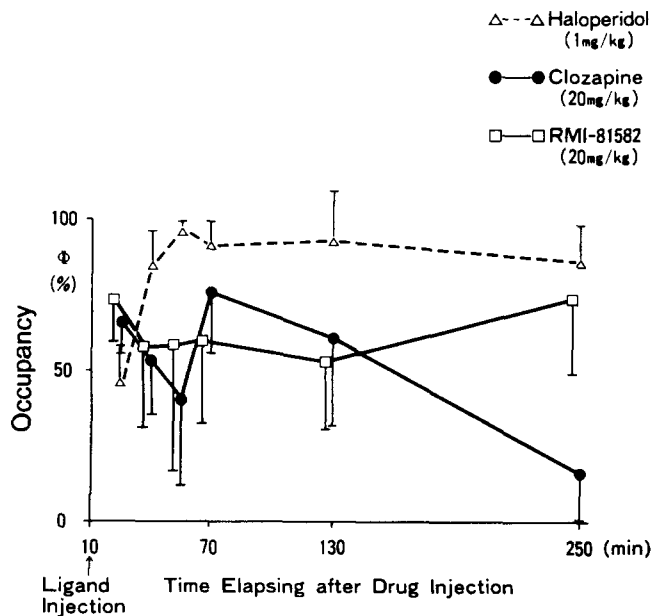


FIG. 2. Time course of D_2 receptor occupancy ($\Phi\%$) in rat frontal cortex after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [^3H]-YM-09151-2 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean \pm 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.

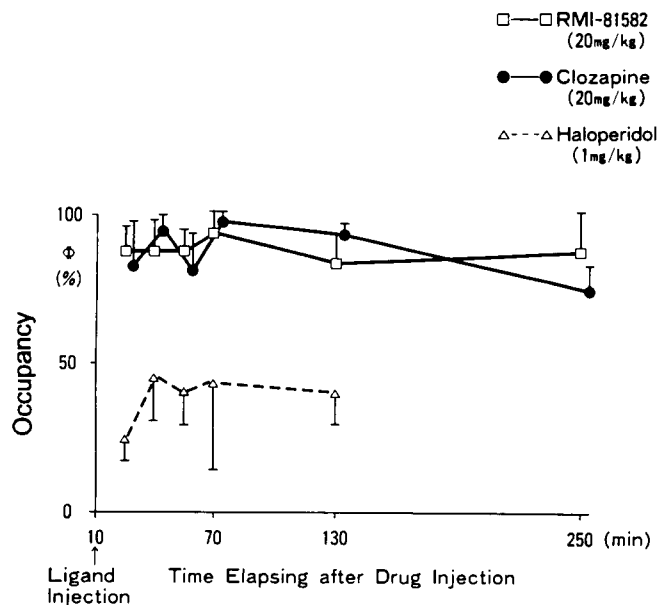


FIG. 3. Time course of 5-HT₂ receptor occupancy (Φ %) in rat frontal cortex after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [³H]-ketanserin (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean \pm 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.

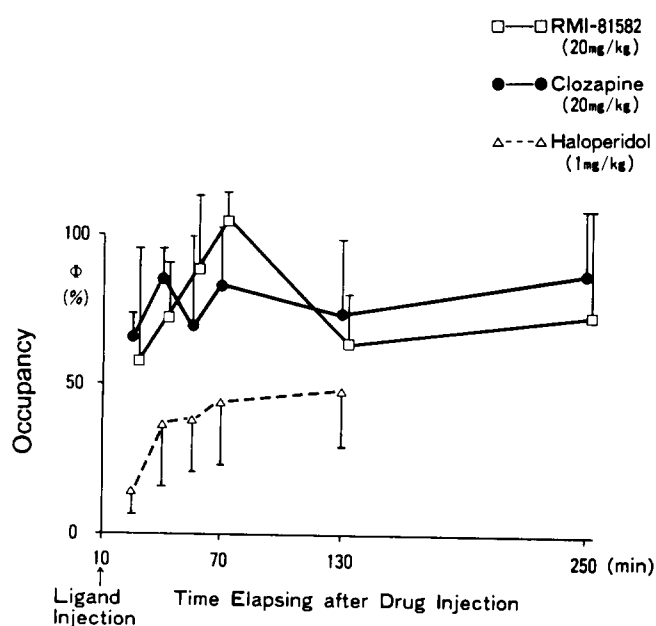


FIG. 4. Time course of 5-HT₂ receptor occupancy (Φ %) in rat striatum after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [³H]-ketanserin (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean \pm 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, striatum of drug-treated rat; X_{nD}, cerebellum of drug-treated rat; X_S, striatum of vehicle-treated rat; X_{nS}, cerebellum of vehicle-treated rat.

dol failed to show stable 5-HT₂ receptor occupancies as late as 240 min after ligand injections (250 min after the drug administrations). Table 1 shows the means of the striatal D₁ and D₂ receptor occupancy including every time point, the means of the frontal 5-HT₂ receptor occupancy calculated without the data at 250 min after the drug administrations, and their ratios (5-HT₂/D₂ ratios of occupancy) for haloperidol, clozapine, and RMI-81582. The latter two drugs marked about 6 to 8 times higher 5-HT₂/D₂ ratios than haloperidol.

DISCUSSION

Little information has been available about the in vivo binding profiles of AAPDs to D₁, D₂, and 5-HT₂ receptors, obtained previously by studies (6,16,24) using the methodology applied in the current investigation.

The present trial differs from these studies in that a 5-HT₂ selective ligand [³H]-ketanserin, D₁ selective [³H]-SCH23390, and D₂ selective [³H]-YM-09151-2 were used. As to the specificity of the ligands, radioactive derivatives of YM-09151-2 and ketanserin have formerly been demonstrated to bind selectively in vivo to D₂ (13) and 5-HT₂ receptors (14), respectively. YM-09151-2 has been shown to have the same order of K_i value for D₄ receptors as for D₂ receptors (29). Considering that the concentration of D₄ mRNA is one to two orders of magnitude lower than that of D₂ (29), the role played by D₄ sites in the total [³H]-YM-09151-2 binding seems to be negligible under the present condition.

[³H]-SCH23390 binding in vivo was also reported to retain the selectivity for D₁ receptors (2). SCH23390 has been indicated to bind also to 5-HT₂ receptors (5,15). Despite this fact,

brain sites labeled by [³H]-SCH23390, which clozapine and RMI-81582 displaced in the current trial, seem to reflect largely D₁ sites, at least in the striatum. One of the reasons for this is that RMI-81582 with a larger affinity for D₁ receptors

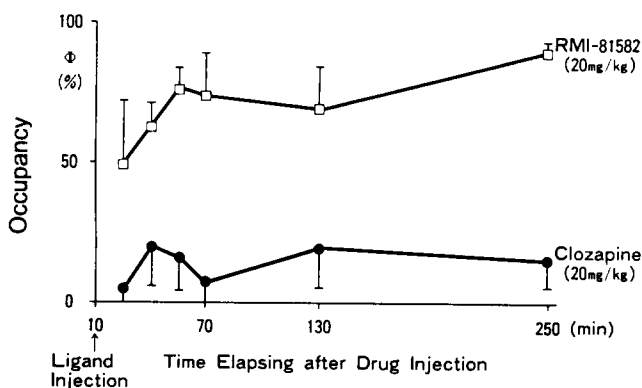


FIG. 5. Time course of D₁ receptor occupancy (Φ %) in rat striatum after single doses of clozapine (20 mg/kg IP) and RMI-81582 (20 mg/kg IP). [³H]-SCH23390 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean \pm SD ($n = 4-5$). $\Phi = [1 - (X_D - X_{nD}) / (X_S - X_{nS})] \times 100(\%)$, where each abbreviation represents radioactivity (% dose/g tissue) of, X_D, striatum of drug-treated rat; X_{nD}, cerebellum of drug-treated rat; X_S, striatum of vehicle-treated rat; X_{nS}, cerebellum of vehicle-treated rat.

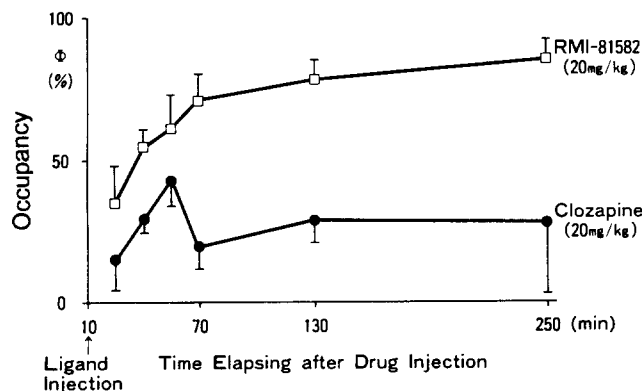


FIG. 6. Time course of D_1 receptor occupancy (Φ %) in rat frontal cortex after single doses of clozapine (20 mg/kg IP) and RMI-81582 (20 mg/kg IP). [3 H]-SCH23390 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean \pm SD ($n = 4-5$). $\Phi = [1 - (X_D - X_{ND}) / (X_S - X_{NS})] \times 100$ (%), 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.

than clozapine, although almost equipotent at 5-HT₂ receptors (18), demonstrated markedly higher occupancy than clozapine for the sites in the D_1 -rich striatum (Fig. 5). Moreover, [11 C]-SCH23390 was used in PET studies to label the central D_1 sites (9,12,26). One of the studies (26) also demonstrated that 1 mg/kg ketanserin does not affect the cortex binding of [3 H]-SCH23390 in vivo in an animal brain. Furthermore, a potent 5-HT₂ antagonist risperidone, revealing only a weak interaction with D_1 receptors (16), failed to show an effective occupancy for striatal and frontal brain sites labeled by [3 H]-SCH23390 under the same condition as the current study (unpublished data).

Receptor occupancies at various time points during an in vivo competition period between the radioligand and the drugs were measured in the current investigation, because binding of ligands with receptors does not reach an equilibrium in vivo as concentrations of free ligands in brain tissue vary time dependently. This could explain that the percent occupation of the respective receptors by the tested drugs varied over the course of 4 h following the ligand injections (Figs. 1–6).

Clozapine 20 mg/kg and RMI-81582 20 mg/kg revealed higher occupancies for 5-HT₂ receptors and lower occupancies for D_2 receptors than haloperidol 1 mg/kg. This finding is in line with our previous data with a larger dose of haloperidol and clozapine (27). The result that AAPDs displayed higher

TABLE 1
MEANS OF STRIATAL D_1 , D_2 AND FRONTAL
5-HT₂ RECEPTOR OCCUPANCY BY ANTIPSYCHOTICS

	D_1 (%)	D_2 (%)	5-HT ₂ (%)	5-HT ₂ / D_2 Ratio
Haloperidol (1 mg/kg)	—	83	37	0.4
Clozapine (20 mg/kg)	13	29	91	3.1
RMI-81582 (20 mg/kg)	71	33	87	2.7

Means of occupancies are calculated with data at 25–250 min (for D_1 , D_2 receptors) and those at 25–130 min (for 5-HT₂ receptors) after the drug administrations, based on the time course studies.

ratios of 5-HT₂ to D_2 in occupancy than haloperidol well reflects the former achievements performed under in vitro (18) and in vivo (24) conditions. In fact, clozapine has recently been shown to occupy frontal 5-HT₂ receptors in schizophrenic patients in a PET study (22). Strong antagonism of 5-HT₂ receptors by AAPDs in vivo may give theoretical endorsement to the clinical view that addition of a 5-HT₂ antagonist to the treatment with antipsychotics like haloperidol reduces EPS (4) and that 5-HT₂ antagonists relieve negative symptoms (10).

It is also worthwhile to note that only clozapine and RMI-81582 showed stable occupancies for D_1 receptors at the current doses tested, although the possibility remains that some part of [3 H]-SCH23390 binds to 5-HT₂ sites, especially in the frontal cortex. This finding seems to be in line with the observation that several AAPDs including clozapine and RMI-81582 show similar attitude toward release and metabolism of dopamine, to D_1 receptor antagonists, suggesting that a mechanism related to D_1 receptor antagonism may contribute to the action of AAPDs (1). The present in vivo binding property of these AAPDs to D_1 receptors may support this proposition.

Although some other pharmacological profiles such as the interaction of clozapine and RMI-81582 with 5-HT₃ sites (3,8) or indirect effects of clozapine on nigral GABAergic mechanisms (7) should be fully considered to explain the therapeutic efficacy of each of these AAPDs, evaluation of in vivo receptor binding properties will help understand the mode of action of AAPDs.

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REFERENCES

- Altar, C. A.; Boyar, W. C.; Wasley, A.; Gerhardt, S. C.; Lieberman, J. M.; Wood, P. L. Dopamine neurochemical profile of atypical antipsychotics resembles that of D_1 antagonists. *Naunyn-Schmiedeberg Arch. Pharmacol.* 338:162–168; 1988.
- Andersen, P. H.; Nielsen, E. B.; Gronvald, F. C.; Braestrup, C. Some atypical neuroleptics inhibit [3 H]SCH23390 binding in vivo. *Eur. J. Pharmacol.* 120:238–236; 1986.
- Ashby, C. R., Jr.; Minabe, Y.; Edward, E.; Wang, R. Y. Comparison of the effects of various typical and atypical antipsychotic drugs on the suppressant action of 2-methylserotonin on medial prefrontal cortical cells in the rat. *Synapse* 8:155–161; 1991.
- Bersani, G.; Grispini, A.; Marini, S.; Pasini, A.; Valducci, M.; Ciani, A. Neuroleptic-induced extrapyramidal side effect: Clinical perspectives with ritanserin (R 55667), a new selective 5-HT₂ receptor blocking agent. *Curr. Ther. Res.* 40:492–499; 1986.
- Bischoff, S.; Heinrich, M.; Krauss, J.; Sills, M. A.; Williams, M.; Vassout, A. Interaction of the D_1 receptor antagonist SCH 23390 with the central 5-HT system: Radioligand binding studies, measurements of biochemical parameters and effects on L-5-HTP syndrome. *J. Recept. Res.* 8:107–120; 1988.
- Bischoff, S. Limbic selective neuroleptics. *Clin. Neuropharmacol.* 15(Suppl. 1):265A–267A; 1992.

7. Coward, D. M.; Imperato, A.; Urwyler, S.; White, T. G. Biochemical and behavioural properties of clozapine. *Psychopharmacology (Berlin) Suppl.* 99:S6-S12; 1989.
8. Edwards, E.; Ashby, C. R., Jr.; Wang, R. Y. The effect of typical and atypical antipsychotic drugs on the stimulation of phosphoinositide hydrolysis produced by the 5-HT₃ receptor agonist 2-methyl-serotonin. *Brain Res.* 545:276-278; 1991.
9. Farde, L.; Nordström, A. L.; Wiesel, F. A.; Pauli, S.; Halldin, C.; Sedvall, G. Positron emission tomographic analysis of central D₁ and D₂ dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: Relation to extrapyramidal side effects. *Arch. Gen. Psychiatry* 49:538-544; 1992.
10. Gelders, Y. G. Thymosthenic agents, a novel approach in the treatment of schizophrenia. *Br. J. Psychiatry* 155(Suppl. 5):33-36; 1989.
11. Goeders, N. E.; Kuhar, M. J. Benzodiazepine receptors binding in vivo with [³H]-Ro 15-1788. *Life Sci.* 37:345-355; 1985.
12. Halldin, C.; Stone-Elander, S.; Farde, L.; Ehrin, E.; Fash, K. J.; Langstrom, B.; Sedvall, G. Preparation of ¹¹C-labelled SCH 23390 for the in vivo study of dopamine D₁ receptors using positron emission tomography. *Appl. Radiat. Isotherm.* 37:1039-1043; 1986.
13. Hatano, K.; Ishikawa, K.; Kawasaki, K.; Hatazawa, J.; Itoh, M.; Ido, T. D₂-Dopamine receptor specific brain uptake of carbon-11-labeled YM-09151-2. *J. Nucl. Med.* 30:515-522; 1989.
14. Laduron, P. M.; Janssen, P. F. M.; Leysen, J. E. In vivo binding of [³H]-ketanserin on serotonin S₂ receptors in rat brain. *Eur. J. Pharmacol.* 81:43-48; 1982.
15. Laruelle, M.; Sidhu, A.; Casanova, M. F.; Weinberger, D. R.; Kleinman, J. E. Characterization of [¹²³I]SCH 23982 binding in human brain: Comparison with [³H]SCH 23390. *Neurosci. Lett.* 131:273-276; 1991.
16. Leysen, J. E.; Janssen, P. M. F.; Gommeren, W.; Wynants, J.; Pauwels, P. J.; Janssen, P. A. J. In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotics risperidone and ocapiperidone. *Mol. Pharmacol.* 41:494-508; 1992.
17. Meltzer, H. Y. Clozapine: Clinical advantage and biochemical mechanism. In: Schultz, C.; Tamminga, C., eds. *Schizophrenia: A scientific focus*. New York: Oxford Press; 1989:302-309.
18. Meltzer, H. Y.; Matsubara, S.; Lee J. C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D₁, D₂ and serotonin₂ pK_i values. *J. Pharmacol. Exp. Ther.* 251:238-246; 1989.
19. Miller, L. G.; Greenblatt, D. J.; Paul, S. M.; Shader, R. I. Benzodiazepine occupancy in vivo: Correlation with brain concentrations and pharmacodynamic action. *J. Pharmacol. Exp. Ther.* 240:516-522; 1987.
20. Nash, J. F.; Meltzer, H. Y.; Gudelsky, G. A. Antagonism of serotonin receptor mediated neuroendocrine and temperature responses by atypical neuroleptics in the rat. *Eur. J. Pharmacol.* 153:309-311; 1988.
21. Neale, R.; Gerhardt, S.; Liebman, J. M. Effect of the novel antipsychotics, RMI-81582 and clozapine, on predictors of extrapyramidal liability in squirrel monkeys. *Drug Dev. Res.* 3:171-176; 1983.
22. Nordström, A. L.; Farde, L.; Halldin, C. High 5-HT₂ receptor occupancy in clozapine treated patients demonstrated by PET. *Psychopharmacology (Berlin)* 110:365-367; 1993.
23. Porsolt, R. D.; Jafre, M. Neuroleptic-induced acute dyskinesias in rhesus monkeys. *Psychopharmacology (Berlin)* 75:16-21; 1981.
24. Stockmeier, C. A.; DiCarlo, J. J.; Zhang, Y.; Thompson, P.; Meltzer, H. Y. Characterization of typical and atypical antipsychotic drugs based on the in vivo of serotonin₂ and dopamine₂ receptors. *J. Pharmacol. Exp. Ther.* 266:1374-1384; 1993.
25. Suhara, T.; Inoue, O.; Kobayashi, K. Effect of desipramine on dopamine receptor binding in vivo. *Life. Sci.* 47:2119-2126; 1990.
26. Suhara, T.; Nakayama, K.; Inoue, O.; Fukuda, H.; Shimizu, M.; Mori, A.; Tatenno, Y. D₁ dopamine receptor binding in mood disorders measured by positron emission tomography. *Psychopharmacology (Berlin)* 106:14-18; 1992.
27. Sumiyoshi, T.; Kido, H.; Sakamoto, H.; Urasaki, K.; Suzuki, K.; Yamaguchi, N.; Mori, H.; Shiba, K.; Yokogawa, K.; Ichimura, F. Time course of dopamine-D₂ and serotonin-5-HT₂ receptor occupancy rates by haloperidol and clozapine in vivo. *Jpn. J. Psychiatr. Neurol.* 47:131-137; 1993.
28. Sumiyoshi, T.; Kido, H.; Sakamoto, H.; Urasaki, K.; Suzuki, K.; Yamaguchi, N.; Mori, H.; Shiba, K.; Yokogawa, K. In vivo dopamine-D₂ and serotonin-5-HT₂ receptor binding study of risperidone and haloperidol. *Pharmacol. Biochem. Behav.* 47:553-557; 1994.
29. Van Tol, H. H. M.; Bunzow, J. R.; Guan, H. C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. Cloning of the gene for a human dopamine D₄ receptor with high affinity for the antipsychotic clozapine. *Nature* 350:610-614; 1991.
30. Wiesel, F. A.; Farde, L.; Nordström, A. L.; Sedvall, G. Central D₁- and D₂-receptor occupancy during antipsychotic drug treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 14:759-767; 1990.
31. Young, M. A.; Meltzer, H. Y. RMI-81582 a novel antipsychotic drug. *Psychopharmacology (Berlin)* 67:101-106; 1980.