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Time Course of Dopamine$_{1,2}$ and Serotonin$_2$ 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 serotonin$_2$ 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 D_1, D_2 and serotonin 5-HT_2 receptors in rat brain with [^{3}H]-SCH23390, [^{3}H]-YM-09151-2, and [^{3}H]-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-HT_2 and lower D_2 receptor occupancies of clozapine and RMI-81582 than those of haloperidol both in the striatum and frontal cortex. The 5-HT_2/D_2 ratios of receptor occupancy for clozapine and RMI-81582 were about 6 to 8 times higher than that for haloperidol. Stable occupancies of D_1 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 D_1, D_2, 5-HT_2 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 D_1 receptors (D_1) (30), higher serotonin 5-HT_2 receptors (5-HT_2)/dopamine D_2 receptors (D_2) 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 D_1, D_2 (2,25) and 5-HT_2 (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 D_1, D_2, and 5-HT_2 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

[^{3}H]-SCH23390 (specific activity 2.78 TBq/mmol), [^{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, 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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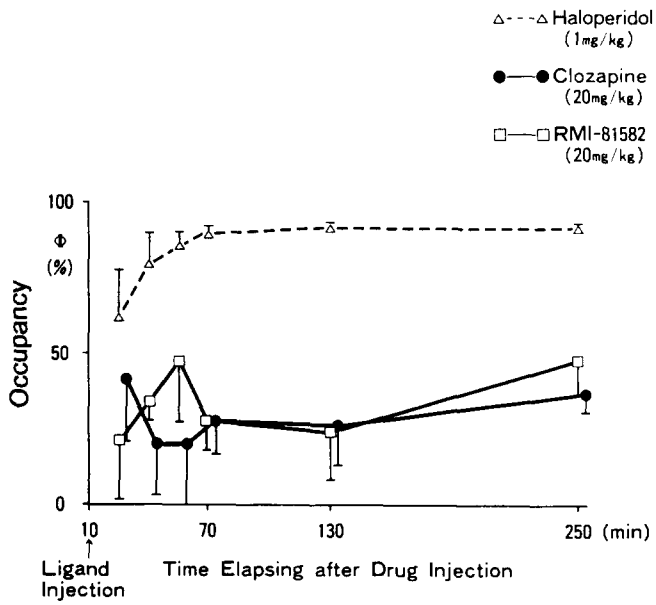

FIG. 1. Time course of D_2 receptor occupancy (Φ%) in rat striatum after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [^{3}H]-YM-09151-2 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents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

doses of the drugs were carefully chosen based on the in vitro affinities for D_2 and clinical dosage. The ligands [^{3}H]-SCH23390 for D_1, [^{3}H]-YM-09151-2 for D_2, or [^{3}H]-ketanserin for 5-HT_2 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 (Φ%) 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.

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-HT_2 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 [^{3}H]-ketanserin). Clozapine, $F(1, 31) = 41.10$, $p < 0.01$, and RMI-81582, $F(1, 31) = 30.73$, $p < 0.01$, revealed higher 5-HT_2 receptor occupancy than haloperidol also in the striatum (comparisons with data at 15–120 min after the injection of [^{3}H]-ketanserin) (Fig. 4). 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 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-

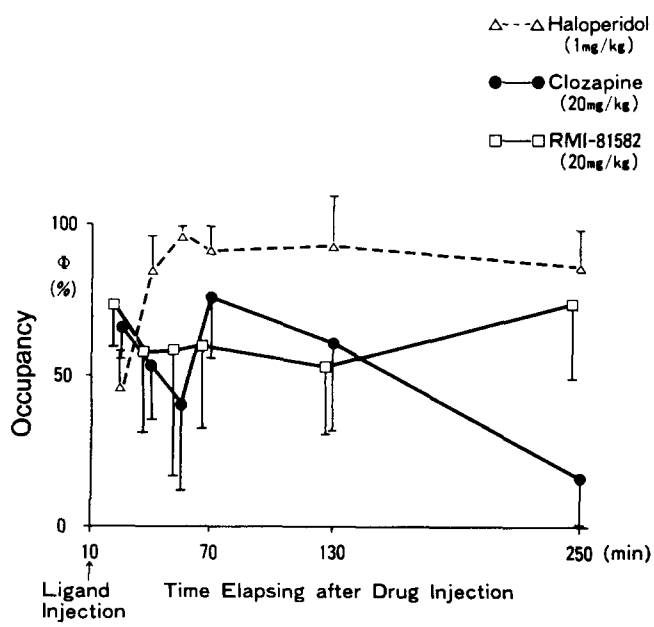

FIG. 2. Time course of D_2 receptor occupancy (Φ%) in rat frontal cortex after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [^{3}H]-YM-09151-2 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point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

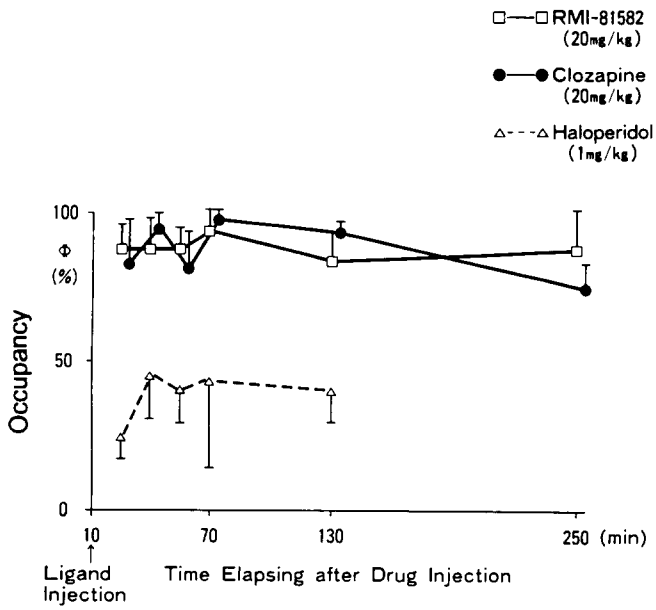

FIG. 3. Time course of 5-HT_2 receptor occupancy (Φ%) in rat frontal cortex after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [^{3}H]-ketanserin (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean ± 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.

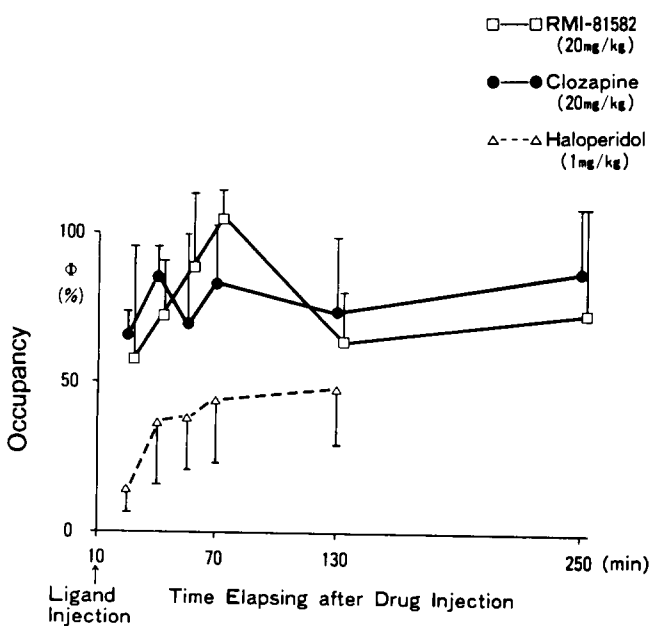

FIG. 4. Time course of 5-HT_2 receptor occupancy (Φ%) in rat striatum after single doses of clozapine (20 mg/kg IP), RMI-81582 (20 mg/kg IP), and haloperidol (1 mg/kg IP). [^{3}H]-ketanserin (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean ± 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-HT_2 receptor occupancies as late as 240 min after ligand injections (250 min after the drug administrations). Table 1 shows the means of the striatal D_1 and D_2 receptor occupancy including every time point, the means of the frontal 5-HT_2 receptor occupancy calculated without the data at 250 min after the drug administrations, and their ratios (5-HT_2/D_2 ratios of occupancy) for haloperidol, clozapine, and RMI-81582. The latter two drugs marked about 6 to 8 times higher 5-HT_2/D_2 ratios than haloperidol.

DISCUSSION

Little information has been available about the in vivo binding profiles of AAPDs to D_1, D_2, and 5-HT_2 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-HT_2 selective ligand [^{3}H]-ketanserin, D_1 selective [^{3}H]-SCH23390, and D_2 selective [^{3}H]-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 D_2 (13) and 5-HT_2 receptors (14), respectively. YM-09151-2 has been shown to have the same order of K_i value for D_4 receptors as for D_2 receptors (29). Considering that the concentration of D_4 mRNA is one to two orders of magnitude lower than that of D_2 (29), the role played by D_4 sites in the total [^{3}H]-YM-09151-2 binding seems to be negligible under the present condition.

[^{3}H]-SCH23390 binding in vivo was also reported to retain the selectivity for D_1 receptors (2). SCH23390 has been indicated to bind also to 5-HT_2 receptors (5,15). Despite this fact, brain sites labeled by [^{3}H]-SCH23390, which clozapine and RMI-81582 displaced in the current trial, seem to reflect largely D_1 sites, at least in the striatum. One of the reasons for this is that RMI-81582 with a larger affinity for D_1 receptors

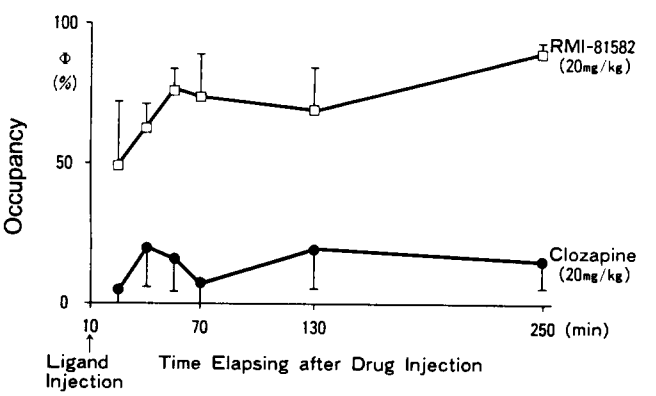

FIG. 5. Time course of D_1 receptor occupancy (Φ%) in rat striatum after single doses of clozapine (20 mg/kg IP) and RMI- 81582 (20 mg/kg IP). [^{3}H]-SCH23390 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean ± SD (n = 4–5).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

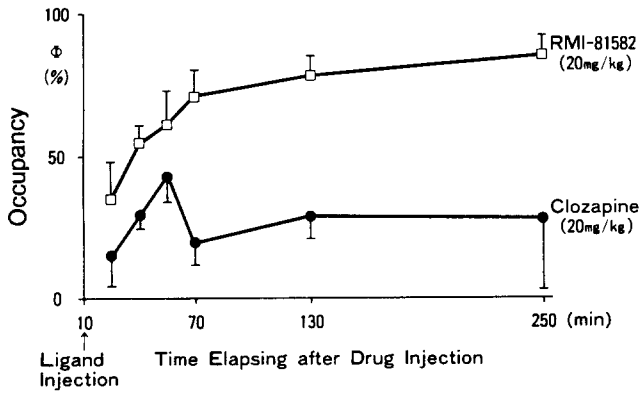

FIG. 6. Time course of D_1 receptor occupancy (Φ%) in rat frontal cortex after single doses of clozapine (20 mg/kg IP) and RMI-81582 (20 mg/kg IP). [^{3}H]-SCH23390 (1.54–1.68 MBq/kg body weight) was injected into a tail vein at 10 min after drug administration. Each point represents the mean ± SD (n = 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.

TABLE 1

MEANS OF STRIATAL D_1, D_2 AND FRONTAL 5-HT_2 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-HT_2 receptors) after the drug administrations, based on the time course studies.

than clozapine, although almost equipotent at 5-HT_2 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-HT_2 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-HT_2 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 ratios of 5-HT_2 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-HT_2 receptors in schizophrenic patients in a PET study (22). Strong antagonism of 5-HT_2 receptors by AAPDs in vivo may give theoretical endorsement to the clinical view that addition of a 5-HT_2 antagonist to the treatment with antipsychotics like haloperidol reduces EPS (4) and that 5-HT_2 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-HT_2 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-HT_3 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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