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Effects of serotonergic agents on the up-regulation of dopamine D_2 receptors induced by haloperidol in rat striatum

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Abstract

We examined the modulatory effect of serotonergic activities on haloperidol-induced up-regulation of dopamine D_2 receptors in rat striatum. Chronic treatment with haloperidol (0.1, 0.5 mg/kg, i.p., 3 weeks) increased the number of dopamine D_2 receptors, while no increase was observed with the atypical antipsychotic drugs clozapine (10 mg/kg) and *trans*-5-chloro-2-methyl-2,3,3*a*,12*b*-tetrahydro-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrolidine maleate (ORG 5222; 0.25 mg/kg). Chronic treatment with 6-chloro-2-(1-piperazinyl)pyrazine (MK-212), a nonselective serotonin (5-hydroxytryptamine, 5-HT) receptor agonist (2.5 mg/kg), or with citalopram, a 5-HT reuptake inhibitor (10 mg/kg), potentiated the haloperidol (0.1 mg/kg)-induced up-regulation of dopamine D_2 receptors, while that with (±)-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), a 5-HT_{1A} receptor agonist (0.1 mg/kg) had no influence on the dopamine D_2 receptor up-regulation. Coadministration of ritanserin (1 mg/kg), a 5-$HT_{2A/2C}$ receptor antagonist, with a low dose of haloperidol (0.1 mg/kg), but not with a high dose of the agent (0.5 mg/kg) attenuated the dopamine D_2 receptor up-regulation. Drug occupation of 5-HT_{2A} and dopamine D_2 receptors in vivo examined using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) was 69.8% and 45.1%, respectively, after the acute administration of haloperidol (0.1 mg/kg) plus ritanserin (1 mg/kg). This profile, that 5-HT_{2A} receptors are highly occupied compared with dopamine D_2 receptors, was similar to that of clozapine or ORG 5222. These results suggest that potent 5-HT_{2A} receptor antagonism versus weak dopamine D_2 receptor blockade may be involved in the absence of up-regulation of dopamine D_2 receptors after chronic treatment with clozapine or ORG 5222.

Keywords: Up-regulation; Dopamine D_2 receptor; Antipsychotic drug, atypical; 5-HT_{2A} receptor; Striatum

1. Introduction

The therapeutic efficacy of antipsychotic drugs is generally attributed to their blockade of dopamine D_2 receptors in the central nervous system (Seeman et al., 1976). Classical (typical) antipsychotic drugs such as haloperidol and chlorpromazine often produce extrapyramidal side effects including parkinsonism-like syndrome and tardive dyskinesia which are thought to be a consequence of dopamine D_2 receptor blockade in the nigrostriatal dopamine system (Klawans et al., 1980). Atypical antipsychotic drugs such as clozapine have been characterized by their low capacity to induce extrapyramidal side effects in humans (Angst et al., 1971) or catalepsy in laboratory rodents (Stille and Hippius, 1971). Another feature of atypical antipsychotic drugs is their unique influence on dopamine D_2 receptor regulation. Thus, chronic administration of typical antipsychotic drugs induces up-regulation of striatal dopamine D_2 receptors, whereas that of atypical antipsychotic drugs does not have such an effect (Lee and Wang, 1984; Rupniak et al., 1985). The dopamine D_2 receptor supersensitivity of the nigrostriatal system may be involved in the development of tardive dyskinesia by classical antipsychotic drugs (Klawans et al., 1980).

There have been many investigations on the property of atypical antipsychotic drugs, but the mechanisms underly-

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ing their atypicality have been uncertain. It has been reported that the lack of extrapyramidal side effects with clozapine could be attributed to its anti-cholinergic properties (Miller and Hiley, 1974). However, all atypical antipsychotic drugs do not necessarily have potent anti-muscarinic effects (Leysen et al., 1993). Moreover, coadministration of anti-cholinergic agents with a typical antipsychotic drug did not prevent the up-regulation of dopamine D_2 receptors in rat striatum (Boyson et al., 1988). Several studies have indicated that dopamine D_1 receptor antagonism may be relevant to the mechanism of atypical antipsychotic drug action (Alter et al., 1988; Farde et al., 1992). As regards dopamine D_2 receptor up-regulation, however, there is a report that dopamine D_1 receptor stimulation but not inhibition attenuates haloperidol-induced up-regulation of dopamine D_2 receptors (Marin and Chase, 1993). Some studies reported that atypical antipsychotic drugs did not unequivocally occupy dopamine D_1 receptors in the rat striatum in vivo (Matsubara et al., 1993).

Serotonergic mechanisms have been shown to affect the extrapyramidal motor functions. Antipsychotic drug-induced catalepsy is attenuated by decreasing serotonergic activities (raphe nucleus destruction, *p*-chlorophenylalanine or nonselective or selective 5-$HT_{2A/2C}$ receptor antagonists pretreatment; Kostowski et al., 1972; Carter and Pycock, 1977; Hicks, 1990), whereas it is potentiated by increasing 5-HT activities (pretreatment with 5-HT reuptake inhibitors or 5-HT_{2A} receptor agonists; Carter and Pycock, 1977). 5-HT_{1A} receptor-mediated mechanisms have been also demonstrated to influence haloperidol-induced catalepsy in rats (Invernizzi et al., 1988; McMillen et al., 1988). Clinical studies reported that ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, or buspirone, a partial 5-HT_{1A} receptor agonist, when administrated in combination with a neuroleptic, attenuated the neuroleptic-induced extrapyramidal side effects in schizophrenic patients (Gelders et al., 1985; Goff et al., 1991). On the other hand, findings on the serotonergic influence on neuroleptic-induced dopamine D_2 receptor up-regulation have been controversial (Saller et al., 1990; Young et al., 1991).

We have previously reported that a certain group of atypical antipsychotic drugs including clozapine was characterized by high affinity for 5-HT_{2A} receptors with lower or minimal affinity for dopamine D_2 receptors both in vitro (Meltzer et al., 1989) and in vivo (Matsubara et al., 1993). These characteristics may be relevant to their weak liability to induce extrapyramidal side effects, and may be involved in the reported absence of dopamine D_2 receptor up-regulation after chronic clozapine treatment. In this study, we examined the effect of serotonergic agents on the dopamine D_2 receptor up-regulation induced by chronic haloperidol treatment, and the possibility that potent 5-HT_{2A} receptor antagonism versus weak dopamine D_2 receptor blockade by atypical antipsychotic drugs may contribute to the lack of dopamine D_2 receptor up-regulation.

2. Materials and methods

2.1. Animals and drugs

Male Wistar rats (120–160 g) supplied from Japan SLC (Shizuoka, Japan) were used for all experiments. [^{3}H]Spiperone (19.1 Ci/mmol) and [^{3}H]ketanserin (60.0 Ci/mmol) were purchased from DuPont New England Nuclear (Boston, MA, USA). *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) was purchased from Aldrich (Milwaukee, WI, USA). (±)-8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and (+)-butaclamol hydrochloride were purchased from Research Biochemicals International (Natick, MA, USA). Methysergide was a generous gift from Dr. H.Y. Meltzer (Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN, USA). The other compounds were generously provided by the manufacturers listed: ketanserin tartrate (Kyowa Hakko Kogyo, Tokyo, Japan); clozapine (Sandoz, Basel, Switzerland); *trans*-5-chloro-2-methyl-2,3,3*a*,12*b*-tetrahydro-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]-pyrrolidine maleate (ORG 5222) (Nippon Organon, Tokyo, Japan); chlorpromazine hydrochloride (Yoshitomi Pharmaceutical, Osaka, Japan); haloperidol (Dainippon Pharmaceutical, Osaka, Japan); 6-chloro-2-(1-piperazinyl)pyrazine (MK-212) (Merck, Rahway, NJ, USA); citalopram (Lundbeck, Copenhaven, Denmark).

2.2. Drug treatments

For chronic administration experiments, the test compound or vehicle (0.15% tartaric acid) was administered i.p. to the rats once a day for 3 weeks. One week after the last injection, the rats were killed by decapitation.

For in vivo receptor occupancy measurements, the rats received test compound or vehicle i.p. 1 h before EEDQ (8 mg/kg; dissolved in water/ethanol, 1:1 (v/v); 4 mg/ml) i.p.. 24 h after EEDQ injection, the rats were killed by decapitation.

The dissected cerebral cortices and striata were frozen on dry ice and stored at −70°C until they were used. The doses of test compounds were basically determined considering the clinical dosage.

2.3. Receptor binding assay

The tissue was homogenized in 50 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.7 at 25°C) containing 5 mM EDTA for 20 s using a Polytron (setting 6.5). The homogenate was centrifuged at 49 000 × *g* for 10 min twice with the intermediate resuspension in the same fresh buffer. The resulting pellet was washed with assay buffer (50 mM Tris-HCl, pH 7.4 at 25°C for dopamine D_2, and pH 7.7 at 25°C for 5-HT_{2A} receptor binding) and centrifuged again. The final pellet was resuspended in these buffers and used for in vivo receptor occupancy measurements and saturation experiments.

The in vivo affinities of the agents for dopamine D_2 receptors in striatum and 5-HT_{2A} receptors in frontal cortex were measured by the method reported previously (Matsubara et al., 1993). Dopamine D_2 and 5-HT_{2A} receptors were labeled with [^{3}H]spiperone and [^{3}H]ketanserin, respectively. The assay mixture for dopamine D_2 binding contained 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbate and 50 nM ketanserin (to block labeling of 5-HT_{2A} receptor sites). Aliquots of the membrane preparations were incubated with two different concentrations of each radioligand (approximately 0.04 and 0.08 nM [^{3}H]spiperone and 0.3 and 0.8 nM [^{3}H]ketanserin) for 15 min at 37°C in 50 mM Tris/HCl buffer. The final tissue concentration was 3 mg of original wet weight tissue per 3 ml for dopamine D_2 and 7 mg/2 ml for 5-HT_{2A} receptor binding. The incubations were terminated by rapid filtration over Whatman GF/B filters, which were rinsed twice with ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25°C) using a harvester. Nonspecific binding was determined in the presence of 1 μM (+)-butaclamol (for dopamine D_2) or 2 μM methysergide (for 5-HT_{2A} receptor binding).

For saturation experiments, six concentrations of [^{3}H]spiperone (0.01–0.32 nM) were used. The final tissue concentration was 2 mg of original wet weight tissue per 3 ml. Assay mixture, incubation, filtration and nonspecific binding were as described above.

Protein concentrations were determined by the method of Lowry et al. (1951).

2.4. Data analysis

Receptor occupancy by a drug was calculated by the following equation: percent occupation = {(drug/EEDQ) − (EEDQ)}/{(drug) − (EEDQ)} × 100, where (drug/EEDQ) represents mean value of specific binding for each site in EEDQ-treated rats with drug pretreatment, (EEDQ) indicates mean value in EEDQ-treated rats with vehicle pretreatment and (drug) indicates mean value in drug-pretreated rats without EEDQ treatment (solvent only) as previously described (Matsubara et al., 1993).

The dissociation constant (K_d) and the total number of binding sites (B_{max}) for [^{3}H]spiperone were estimated from saturation experiments using the non-linear regression program EBDA/LIGAND. Statistical comparisons were made by analysis of variance followed by a Duncan new multiple range test.

3. Results

Chronic treatment with haloperidol (0.1, 0.5 mg/kg) or chlorpromazine (10 mg/kg) significantly increased the number of dopamine D_2 receptors in the striatum compared with control, while no increase was observed with clozapine (10 mg/kg) or ORG 5222 (0.25 mg/kg) treatment (Fig. 1). Three-week administration of MK-212 (2.5 mg/kg), a nonselective 5-HT receptor agonist, or citalopram (10 mg/kg), a 5-HT reuptake inhibitor, both of which had no effect on the number of dopamine D_2

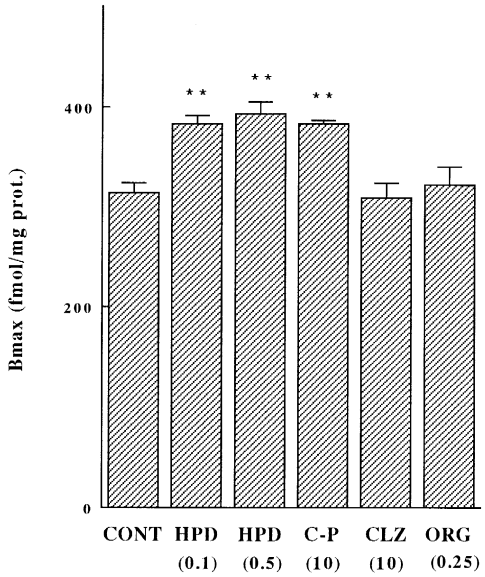

Fig. 1. Effects of chronic treatment with haloperidol (HPD), chlorpromazine (C-P), clozapine (CLZ) and ORG 5222 (ORG) on the densities of dopamine D_2 receptors in rat striatum. Animals were treated once a day for 3 weeks with vehicle (CONT), HPD (0.1, 0.5 mg/kg, i.p.), C-P (10 mg/kg, i.p.), CLZ (1 mg/kg, i.p.) or ORG 5222 (0.25 mg/kg, i.p.), and were decapitated 1 week after the last injection. The total number of binding sites (B_{max}) and the dissociation constant (K_d) for [^{3}H]spiperone were estimated from saturation experiments using Scatchard analysis. Each value is the mean ± S.E.M ($n = 6$). $^{**}P < 0.01$ vs. CONT.

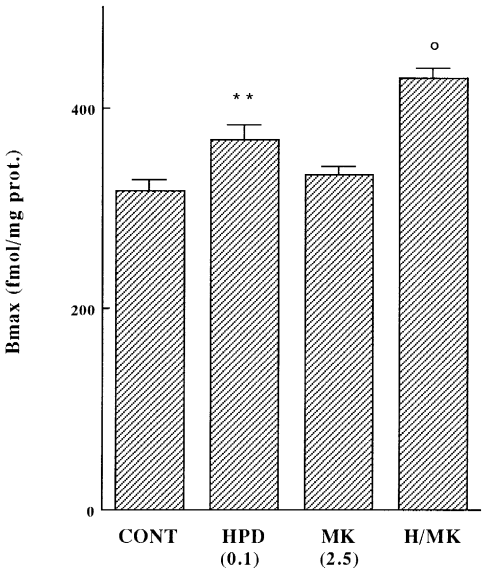

Fig. 2. Effects of chronic treatment with haloperidol (HPD), MK-212 (MK) and haloperidol/MK-212 (H/MK) on the densities of dopamine D_2 receptors in rat striatum. Animals were treated once a day for 3 weeks with vehicle (CONT), HPD (0.1 mg/kg, i.p.), MK (2.5 mg/kg, i.p.) or HPD and MK (0.1 mg/kg and 2.5 mg/kg, respectively, i.p.), and were decapitated 1 week after the last injection. Each value is the mean ± S.E.M ($n = 6$). $^{**}P < 0.01$ vs. CONT. $^{\circ}P < 0.05$ vs. HPD.

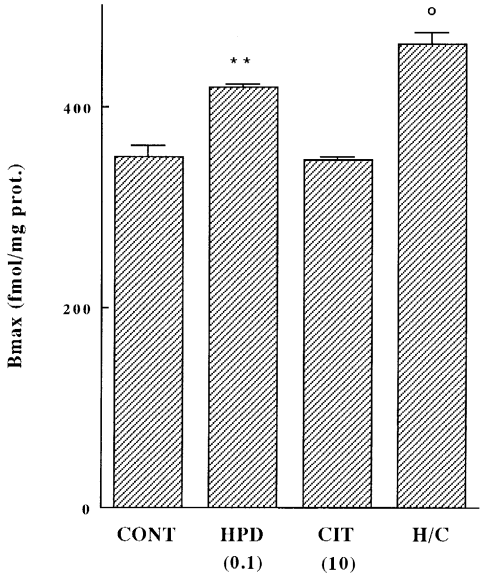

Fig. 3. Effects of chronic treatment with haloperidol (HPD), citalopram (CIT) and haloperidol/citalopram (H/C) on the densities of dopamine D_2 receptors in rat striatum. Animals were treated once a day for 3 weeks with vehicle (CONT), HPD (0.1 mg/kg, i.p.), CIT (10 mg/kg, i.p.) or HPD and CIT (0.1 mg/kg and 10 mg/kg, respectively, i.p.), and were decapitated 1 week after the last injection. Each value is the mean ± S.E.M ($n = 6$). $^{**}P < 0.01$ vs. CONT. $^{\circ}P < 0.05$ vs. HPD.

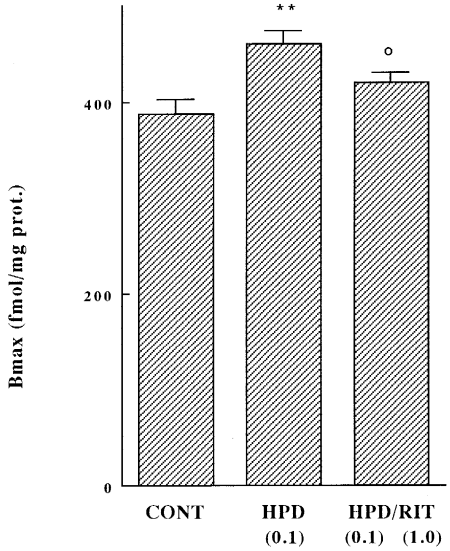

Fig. 5. Effects of chronic treatment with haloperidol (HPD) and haloperidol/ritanserin (HPD/RIT) on the densities of dopamine D_2 receptors in rat striatum. Animals were treated once a day for 3 weeks with vehicle (CONT), HPD (0.1 mg/kg, i.p.) or HPD and RIT (0.1 mg/kg and 1.0 mg/kg, respectively, i.p.), and were decapitated 1 week after the last injection. Each value is the mean ± S.E.M ($n = 8$). $^{**}P < 0.01$ vs. CONT. $^{\circ}P < 0.05$ vs. HPD.

receptor sites by themselves, potentiated the up-regulation of dopamine D_2 receptors induced by haloperidol (0.1 mg/kg; Figs. 2 and 3). Similar results were obtained when chronically coadministrated with 0.5 mg/kg of haloperidol (data not shown). Chronic treatment with ritanserin (1 mg/kg), a 5-$HT_{2A/2C}$ receptor antagonist, had no effect on the number of dopamine D_2 receptor sites (Fig. 4). Coadministration of ritanserin with haloperidol (0.5 mg/kg) had no influence on the haloperidol-induced increase in dopamine D_2 receptor sites (Fig. 4), but that with lower dose of haloperidol (0.1 mg/kg) significantly atten-

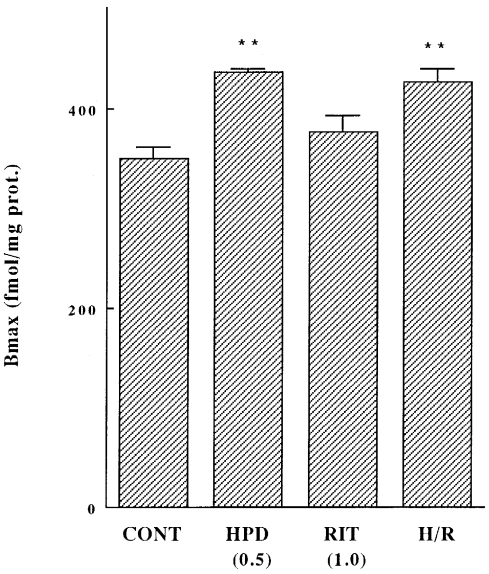

Fig. 4. Effects of chronic treatment with haloperidol (HPD), ritanserin (RIT) and haloperidol/ritanserin (H/R) on the densities of dopamine D_2 receptors in rat striatum. Animals were treated once a day for 3 weeks with vehicle (CONT), HPD (0.5 mg/kg, i.p.), RIT (1.0 mg/kg, i.p.) or HPD and RIT (0.5 mg/kg and 1.0 mg/kg, respectively, i.p.), and were decapitated 1 week after the last injection. Each value is the mean ± S.E.M ($n = 6$). $^{**}P < 0.01$ vs. CONT.

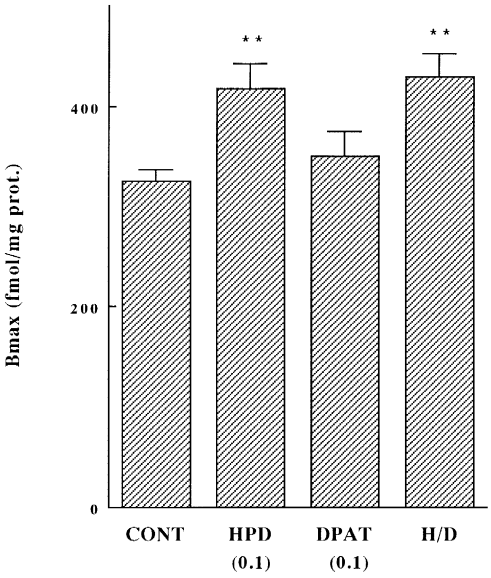

Fig. 6. Effects of chronic treatment with haloperidol (HPD), 8-OH-DPAT (DPAT) and haloperidol/8-OH-DPAT (H/D) on the densities of dopamine D_2 receptors in rat striatum. Animals were treated once a day for 3 weeks with vehicle (CONT), HPD (0.1 mg/kg, i.p.), DPAT (0.1 mg/kg, i.p.) or HPD and DPAT (0.1 mg/kg and 0.1 mg/kg, respectively, i.p.), and were decapitated 1 week after the last injection. Each value is the mean ± S.E.M ($n = 6$). $^{**}P < 0.01$ vs. CONT.

Table 1
Percent occupation of 5-HT_{2A} and dopamine D_2 receptors by various drugs in vivo

Drug	5-HT_{2A} (%)	D_2 (%)
C-P (10 mg/kg)	63.4	61.4
HPD (0.1 mg/kg)	0	44.3
HPD (0.5 mg/kg)	0	68.0
Clozapine (10 mg/kg)	50.5	10.9
ORG 5222 (0.25 mg/kg)	83.7	43.8
HPD (0.1 mg/kg) and RIT (1 mg/kg)	69.8	45.1
HPD (0.5 mg/kg) and RIT (1 mg/kg)	75.6	73.6

Animals received test compound or vehicle i.p. 1 h before EEDQ (8 mg/kg) i.p. and were decapitated 24 h after the EEDQ injection. Percent receptor occupation was calculated by the following equation as described in Section 2: % occupation = {(drug/EEDQ) − (EEDQ)}/{(drug) − (EEDQ)} × 100. C-P, chlorpromazine; HPD, haloperidol; CLZ, clozapine; RIT, ritanserin.

uated the dopamine D_2 receptor up-regulation (Fig. 5). Chronic administration of 8-OH-DPAT, a 5-HT_{1A} receptor agonist (0.1 mg/kg), had no influence on the haloperidol (0.1 mg/kg)-induced increase in dopamine D_2 receptor sites (Fig. 6). No significant difference was found in K_d value for [^{3}H]spiperone binding among treatment groups in all experiments.

The in vivo occupation of 5-HT_{2A} and dopamine D_2 receptors after the acute coadministration of ritanserin (1 mg/kg) with haloperidol (0.5 mg/kg) was 75.6% and 73.6%, respectively (Table 1). Coadministration with a lower dose of haloperidol (0.1 mg/kg), on the other hand, showed high occupation of 5-HT_{2A} receptors (69.8%) with considerably smaller occupation of dopamine D_2 receptors (45.1%) (Table 1). This potent 5-HT_{2A} receptor blockade versus weak dopamine D_2 receptor antagonism was similar to the profile of clozapine and ORG 5222 (Table 1). The dopamine D_2 receptors were 44.3% and 68.0% occupied by 0.1 mg/kg and 0.5 mg/kg haloperidol alone, respectively, which was almost the same when ritanserin (1 mg/kg) was added (Table 1).

4. Discussion

The present results indicate that chronic treatment with a 5-HT receptor agonist, MK-212, or a 5-HT reuptake inhibitor, citalopram, potentiated the up-regulation of dopamine D_2 receptors when coadministrated with haloperidol (0.1 mg/kg). Moreover, coadministration of the 5-$HT_{2A/2C}$ receptor antagonist ritanserin with a low dose of haloperidol (0.1 mg/kg) but not with a high dose (0.5 mg/kg) of the agent significantly attenuated the dopamine D_2 receptor up-regulation induced by haloperidol alone. Cotreatment with the 5-HT_{1A} receptor agonist 8-OH-DPAT was without effect on the haloperidol (0.1 mg/kg)-induced up-regulation of dopamine D_2 receptors. Chronic administration of clozapine and ORG 5222, an atypical antipsychotic drug candidate, did not up-regulate the striatal dopamine D_2 receptors. Moreover, the profile of 5-HT_{2A} and dopamine D_2 receptor occupation in vivo after the acute coadministration of ritanserin with a high dose (0.5 mg/kg) of haloperidol was comparable with that of the typical antipsychotic drug chlorpromazine, whereas that of ritanserin plus a low dose (0.1 mg/kg) of haloperidol was similar to those of clozapine and ORG 5222, in line with the observation that 5-HT_{2A} receptors were more potently antagonized than dopamine D_2 receptors.

It has been known that chronic administration of a typical antipsychotic drug produces an up-regulation of striatal dopamine D_2 receptors (Seeger et al., 1982), which may contribute to the adverse effects of neuroleptic treatment on motor function. On the other hand, chronic treatment with an atypical antipsychotic drug, clozapine, which has a low incidence of extrapyramidal side effects (Angst et al., 1971) and tardive dyskinesia (Klawans et al., 1980), does not induce the increase in dopamine D_2 receptors in rat striatum (Wilmot and Szczepanik, 1989). The present study reconfirms this finding and extends it to ORG 5222, an atypical antipsychotic drug candidate.

Biochemical (Saller et al., 1990), electrophysiological (Fibiger and Miller, 1977; Ugedo et al., 1989) and behavioral studies (Invernizzi et al., 1988; Kulikov et al., 1994) suggest that functional interactions occur between brain serotonergic and dopaminergic systems. As regards extrapyramidal motor functions, antipsychotic drug-induced catalepsy is attenuated by decreasing serotonergic activities (Carter and Pycock, 1977; Kostowski et al., 1972). Conversely, it is potentiated by increasing serotonergic activities (Carter and Pycock, 1977). It has also been reported that extrapyramidal side effects induced by haloperidol were attenuated by cotreatment with ritanserin in schizophrenic patients (Bersani et al., 1986). Several studies have recently indicated that 5-HT_{1A} receptor agonists such as 8-OH-DPAT reduced the catalepsy induced by haloperidol in rats (Invernizzi et al., 1988; McMillen et al., 1988). It was also reported that buspirone, a 5-HT_{1A} receptor partial agonist, improved extrapyramidal side effects when added to neuroleptics in schizophrenic patients (Goff et al., 1991) (see also Section 1).

There have been controversial findings on the serotonergic influence on neuroleptic-induced up-regulation of striatal dopamine D_2 receptors. Saller et al. (1990) found that coadministration of a 5-HT_{2A} receptor antagonist with haloperidol attenuated the dopamine D_2 receptor up-regulation. Young et al. (1991) reported that subchronic treatments with buspirone (5-HT_{1A} receptor partial agonist), mesulergine (5-$HT_{2A/2C}$ receptor antagonist) and ICS 205-930 (5-HT_3 receptor antagonist) had no effect on the increase in dopamine D_2 receptor sites by haloperidol.

In the present study, we found that haloperidol-induced dopamine D_2 receptor up-regulation was potentiated by increasing serotonergic activity (i.e., cotreatment with a 5-HT receptor agonist or a selective 5-HT reuptake inhibitor), while it was attenuated by a 5-$HT_{2A/2C}$ receptor

antagonist. However, this attenuation was observed only when ritanserin was coadministrated with 0.1 mg/kg of haloperidol. A 5-HT_{1A} receptor agonist had no effect on the up-regulation. In the EEDQ experiments, acute coadministration of ritanserin with a low dose of haloperidol (0.1 mg/kg) exhibited higher occupation of 5-HT_{2A} receptors (69.8%) than dopamine D_2 receptors (45.1%), but that with a higher dose of haloperidol (0.5 mg/kg) exhibited high occupation of both receptors (75.6% and 73.6%, respectively). The former profile is similar to those of atypical antipsychotic drugs such as clozapine and ORG 5222, while the latter is comparable with that of a typical antipsychotic drug such as chlorpromazine. These findings suggest that 5-HT_{2A} receptor blockade would be expected to attenuate the development of dopamine D_2 receptor supersensitivity so long as the blockade of 5-HT_{2A} receptors is more potent than that of dopamine D_2 receptors. This may well explain the discrepancy between the findings by Saller et al. (1990) and Young et al. (1991). The former authors used 0.25 mg/kg of haloperidol and found attenuation of dopamine D_2 receptor up-regulation by coadministration of a 5-HT_{2A} receptor antagonist, whereas the latter authors used 2 mg/kg of haloperidol and found no effect on the haloperidol-induced dopamine D_2 receptor up-regulation by the 5-$HT_{2A/2C}$ receptor antagonist. Similarly, neurochemical studies also suggested such a possibility that relative antagonism against 5-HT_{2A} versus dopamine D_2 receptors may be relevant to the development of dopamine D_2 receptor up-regulation by chronic antipsychotic drug treatment. The coadministration of ICI169,369, a 5-HT_{2A} receptor antagonist, with 0.25 mg/kg haloperidol was reported to enhance the compensatory increase in striatal dopamine metabolism by haloperidol (Saller et al., 1990), whereas that of 0.5 mg/kg ritanserin with a higher dose (0.5 mg/kg) of haloperidol did not affect the haloperidol-induced changes in dopamine metabolism (Lappalainen et al., 1990). Saller et al. (1990) suggested the possibility that 5-HT_{2A} receptor blockade, by enhancing dopamine metabolism, may act to attenuate the blockade of striatal dopamine D_2 receptors. These mechanisms may also explain the finding of Wadenberg (1992) that dopamine D_2 receptor antagonist raclopride (16 mg/kg)-induced catalepsy could not be antagonized by treatment with ritanserin (0.13–2.0 mg/kg).

The precise mechanism by which 5-HT_{2A} receptor antagonism may attenuate the dopamine D_2 receptor up-regulation induced by haloperidol is uncertain from the present data. One possible explanation may be that 5-HT_{2A} receptor antagonism affects raphe neurons which then influence neuronal dopamine function. It was reported that lesion of the dorsal raphe nucleus resulted in increases in the dopamine metabolites in the substantia nigra, suggesting a tonically active inhibition of dopamine neurons from dorsal raphe (Dray et al., 1976; Nicolaou et al., 1979). It was also reported that acute ritanserin treatment increased both the burst firing rate of midbrain dopamine neurons (Ugedo et al., 1989). Dopamine receptor agonist administration was reported to attenuate haloperidol-induced dopamine D_2 receptor supersensitivity (List and Seeman, 1979).

In conclusion, our study indicates that 5-HT_{2A} receptor blockade attenuates the dopamine D_2 receptor up-regulation induced by haloperidol, so long as the blockade of dopamine D_2 receptors is less potent than that of 5-HT_{2A} receptors. This finding supports our previous reports that high affinity for 5-HT_{2A} receptors with lower effect on dopamine D_2 receptors both in vitro and in vivo may be relevant to the atypicality for a certain group of antipsychotic drugs (Matsubara et al., 1993; Meltzer et al., 1989). These characteristics may underlie not only the weak extrapyramidal side effect-producing property but also the absence of striatal dopamine D_2 receptor up-regulation after the chronic treatment with this type of atypical antipsychotic drugs.

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