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SR46349-B, a 5-$HT_{2A/2C}$ Receptor Antagonist, Potentiates Haloperidol-induced Dopamine Release in Rat Medial Prefrontal Cortex and Nucleus Accumbens

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The combination of M100907, a putative antipsychotic drug (APD) and serotonin (5-$HT)_{2A}$ antagonist, and the typical APD haloperidol, can enhance dopamine (DA) release in rat medial prefrontal cortex (mPFC), an effect which has been postulated to be of value to improve cognition and negative symptoms. The present study demonstrated that another putative APD and 5-$HT_{2A/2C}$ antagonist, SR46349-B (10 mg/kg, but not 1–3 mg/kg) alone, but not M100907 (0.1 and 3 mg/kg) alone, increased mPFC DA release, whereas neither drug alone affected nucleus accumbens (NAC) DA release. Neither SR46349-B nor M100907 alone affected nucleus accumbens (NAC) DA release. Neither SR46349-B nor M100907 alone affected nucleus accumbens (NAC) DA release. SR46349-B (3 mg/kg) potentiated haloperidol-induced DA release in both regions, whereas M100907 (0.1 mg/kg) potentiated haloperidol (0.1 mg/kg)-induced mPFC DA release and inhibited it in the NAC. WAY100635 (0.2 mg/kg), a 5-HT_{1A} antagonist, abolished the effects of haloperidol plus M100907 as well as SR46349-B on DA release in the mPFC, but did not do so in the NAC. Thus, 5-HT_{2A} and 5-$HT_{2A/2C}$ antagonism together with haloperidol-induced D_2 antagonism may potentiate mPFC DA release via 5-HT_{1A} agonism, whereas the combined effects of these agents on NAC DA release is not dependent upon 5-HT_{1A} receptor stimulation. Interestingly, similar to the effect of SR46349-B, high dose M100907 (3 mg/kg), which might have antagonist activity at 5-HT_{2C} receptors, potentiated 1 mg/kg haloperidol-induced DA release in the mPFC and NAC. These results suggest that 5-$HT_{2A/2C}$ antagonism may be more advantageous than selective 5-HT_{2A} antagonism as an adjunct to D_2 antagonists to improve cognition and negative symptoms in schizophrenia.
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KEY WORDS: *5-HT_{2A} receptor antagonism; 5-HT_{2C} receptor antagonism; 5-HT_{1A} receptor agonism; Haloperidol; Dopamine release; Medial prefrontal cortex; Nucleus accumbens*

Potent serotonin (5-$HT)_{2A}$ antagonism, in relation to weaker dopamine (DA) D_2 receptor antagonism, has been suggested to distinguish the atypical antipsychotic drugs (APD) such as clozapine, quetiapine, olanzapine, risperidone, and ziprasidone, from the typical APDs haloperidol or S(-)-sulpiride, and to be a major factor contributing to their antipsychotic action and low liability of causing extrapyramidal symptoms (EPS) (Meltzer

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et al. 1989; Schotte et al. 1996; Ichikawa and Meltzer 1999a; Meltzer 1999). The atypical APDs have a greater ability than the typical APDs to increase cortical DA release in rodents and non-human primates (Moghaddam and Bunney 1990; Li et al. 1998; Kuroki et al. 1999), which may contribute to their greater ability to improve negative and cognitive symptoms in patients with schizophrenia (Meltzer and McGurk 1999), although other factors may also contribute; e.g. adrenergic (Hertel et al. 1999) and muscarinic cholinergic mechanisms (Goff et al. 1995; Bymaster et al. 1999; Tandon 1999; Ichikawa et al. 2002).

Clozapine, olanzapine, and risperidone, all of which are 5-HT_{2A} and D_2 receptor antagonists, enhance DA release in rat medial prefrontal cortex (mPFC), and this effect has been shown to be related to the combined 5-HT_{2A} and D_2 receptor blockade (Kuroki et al. 1999; Ichikawa et al. 2001a,b). We have also found that the selective 5-HT_{2A} receptor antagonist M100907 (Carr et al. 1991; Kehne et al. 1996) potentiated the ability of low (0.1 mg/kg), but not high dose (1 mg/kg) haloperidol to increase DA release in the mPFC, and that M100907, reciprocally, inhibited the ability of both doses of haloperidol to increase DA release in the nucleus accumbens (NAC) (Liégeois et al. 2002). Thus, when a 5-HT_{2A} receptor antagonist is combined with typical APDs such as haloperidol, which is devoid of appreciable 5-HT_{2A} receptor antagonism in vitro and in vivo (Meltzer et al. 1989; Stockmeier et al. 1993; Matsubara et al. 1993; Schotte et al. 1996), it would be expected to produce increases in cortical DA release comparable to atypical APDs. Interestingly, ritanserin, a mixed 5-$HT_{2A/2C}$ receptor antagonist (Roth et al. 1992), has been reported to potentiate the $D_{2/3}$ receptor antagonist raclopride-induced DA release in the mPFC and NAC, but not striatum (STR) (Andersson et al. 1995). It has also been reported that ritanserin and M100907 both potentiated the raclopride-induced conditioned avoidance response (CAR) in rats, a model for antipsychotic action (Andersson et al. 1995; Wadenberg et al. 1998). M100907 also potentiated haloperidol-induced CAR following its systemic or direct administration into either the mPFC or NAC (Hicks et al. 1999; Wadenberg et al. 2001). Taken together, these results suggest that 5-HT_{2A} receptor antagonism may increase antipsychotic effects of typical APDs such as haloperidol, which lack appreciable affinity for the 5-HT_{2A} receptor (Ichikawa and Meltzer 1999a; Meltzer 1999).

Recent microdialysis studies have suggested different and sometimes opposite effects of 5-HT_{2A} and 5-HT_{2C} receptor on cortical, striatal, and NAC DA release (Ichikawa and Meltzer 1999a; Di Matteo et al. 2001). For example, the selective 5-HT_{2C} receptor antagonist SB242084 increased DA release in the mPFC (Millan et al. 1998) and NAC (Di Matteo et al. 1999, 2000a,b; Gobert et al. 2000), but not the STR (Di Matteo et al. 1999), whereas M100907 had no effect on DA release in either the mPFC or the NAC (Gobert and Millan 1999; Ichikawa and Meltzer 2000; Rollema et al. 2000; Zhang et al. 2000; Ichikawa et al. 2001a,b; Pehek et al. 2001; Westerink et al. 2001; Liégeois et al. 2002). The selective 5-HT_{2C} receptor agonist Ro 60-0175 decreased DA release in the mPFC (Gobert et al. 2000; Ichikawa et al. 2001b) and NAC (Di Matteo et al. 1999, 2000a,b), but not STR (Di Matteo et al. 1999), whereas 5-HT_{2A} receptor stimulation by DOI, a 5-$HT_{2A/2C}$ receptor agonist, increased DA release in the mPFC (Gobert and Millan 1999; Ichikawa et al. 2001b) and NAC (Yan 2000; Yan et al. 2000).

Another 5-HT_{2A} and possibly also 5-HT_{2C} receptor antagonist, SR46439-B (IC_{50} = 120 nM for 5-HT_{2C} receptors in pig cortex, and 5.8 nM for 5-HT_{2A} receptors in rat cortex, Rinaldi-Carmona et al. 1992), which alone had no effect on DA release in the STR, has been reported to inhibit the ability of haloperidol (0.01, but not 0.1 or 1.0, mg/kg) to increase striatal DA release (Spampinato et al. 1998; Lucas and Spampinato 2000). However, there are no data on its effect on basal and haloperidol-induced DA release in the mPFC and NAC. SR46349-B may be effective in the treatment of schizophrenia (Arvarytis L, personal communication), while the therapeutic effects of M100907 (Shipley 1998; Talvik-Lotfi et al. 2000) and ritanserin (Wiesel et al. 1994) are not so apparent. Therefore, it is of considerable interest whether SR46349-B has an effect on basal and haloperidol-induced DA release in the mPFC and NAC similar to that of M100907, ritanserin, or not.

We have also suggested that the atypical APDs, such as clozapine, olanzapine, and risperidone, increase DA release in the mPFC, at least in part, via 5-HT_{1A} receptor stimulation, because 5-HT_{1A} receptor agonist R(+)-8-OH-DPAT dose-dependently increases DA release in the mPFC, and WAY100635, a selective 5-HT_{1A} receptor antagonist, inhibits those effects of R(+)-8-OH-DPAT and the three atypical APDs (Ichikawa et al. 2001a). The facilitation of 5-HT_{1A} receptor stimulation by clozapine, olanzapine, and risperidone regarding the effect on DA release in the mPFC may be associated with their concomitant blockade of 5-HT_{2A} and D_2 receptors. In this regard, M100907, a selective 5-HT_{2A} receptor antagonist, potentiated the $D_{2/3}$ receptor antagonist S(-)-sulpiride-induced DA release in the mPFC, an effect completely abolished by WAY100635 (Ichikawa et al. 2001a). Therefore, it is possible that, as has been shown by the combination with M100907 (Liégeois et al. 2002), 5-HT_{2A} receptor antagonism by SR46349-B also potentiates the ability of haloperidol to produce minimal increases in DA release in the mPFC. It is also possible that these potentiations by M100907 and SR 46349-B are mediated via functional 5-HT_{1A} receptor agonism due to combined 5-HT_{2A} and D_2 receptor blockade (Ichikawa et al. 2001a).

The present study examined the effect of SR46349-B, a 5-HT_{2A} receptor antagonist, on basal and haloperidol-induced DA release in the mPFC and NAC, compared with the effects of M100907. We also tested the hypothesis that SR46349-B as well as M100907 affects the ability of haloperidol to increase DA release in the mPFC and NAC via 5-HT_{1A} receptor-dependent mechanism(s).

METHODS AND MATERIALS

Animals

Male Sprague-Dawley albino rats (Zivic-Miller Laboratories, Porterville, PA) weighing 250 to 350 g were housed two to three per cage and maintained in a controlled 12:12-h light-dark cycle (lights on at 7:00 A.M.) and under constant temperature at 22°C, with free access to food and water.

Surgery and Microdialysis

The procedure employed here has been reported elsewhere (Ichikawa et al. 2001a,b). In brief, three to five days following cannulation surgery under anesthesia with a combination of xylazine (13 mg/kg, Rompun; Shawnee Mission, KS) and ketamine HCl (87 mg/kg, Ketaset; Fort Dodge Laboratories, Fort Dodge, IA), a dialysis probe (2 mm membrane length) was implanted into the mPFC and NAC. Stereotaxic coordinates of probe, when implanted, are A +3.2, L −0.8, V -5.5 mm for the mPFC, and A +2.0, L +1.5, V −7.5 mm for the NAC, respectively, relative to bregma (Paxinos and Watson 1986). A catheter constructed from microbore Tygon tubing (TGY-010; Small Parts Inc., Miami Lakes, FL) was implanted subcutaneously in the back of rats. After the overnight perfusion (0.4 μl/min) of the probe, the flow rate was increased to 1.5 μl/min, and dialysate samples were collected every 30 min. The perfusion medium was Dulbecco's phosphate buffered saline solution (Sigma, St. Louis, MO) including Ca^{2+} (138 mM NaCl, 8.1 mM Na_2HPO_4, 2.7 mM KCl, 1.5 mM KH_2PO_4, 0.5 mM MgCl, 1.2 mM $CaCl_2$, pH 7.4). The location of the dialysis probes was verified with 100 μm brain slices (OTS-4000; FHC, Bowdoinham, ME). The Institutional Animal Care and Use Committee of Vanderbilt University approved the procedure applied in these experiments.

Biochemical Assay

Dialysate samples (45 μl/30 min) were directly applied onto a HPLC with a 20 μl sample loop and analyzed for DA with a Millennium chromatogram manager (Waters, Milford, MA). DA was separated on a C18 reversed phase column (BDS Hypersil, 3 μm, 1 × 100 mm; Keystone Scientific, Bellefonte, PA) at 35°C. The mobile phase consisted of 48 mM anhydrous citric acid and 24 mM sodium acetate trihydrate containing 0.5 mM EDTA-Na_2, 10 mM NaCl, 2 mM dodecyl sulfate sodium salt (Acros, Pittsburgh, PA) and 17% (v/v) acetonitrile, adjusted to pH 4.8 with concentrated NaOH, and was pumped at 0.05 ml/min (LC-10AD; Shimadzu, Kyoto, Japan). DA was detected by a 3-mm glassy carbon unijet working electrode (MF-1003, BAS) set at +0.58 V (LC-4C, BAS) versus an Ag/AgCl reference electrode.

Drugs

WAY100635 (Sandoz, Basel, Switzerland) was dissolved in deionized water. Haloperidol (McNeil, Spring House, PA) and M100907 (Hoechst Marion Roussel, NJ) were dissolved in 0.1 M tartaric acid solution, which was adjusted to pH 6–7 with NaOH. SR46349-B (Sanofi, Montpellier, France) was dissolved in 45% 2-hydroxypropyl-β-cyclodextrin (Research Biochemical Inc., Natick, MA). Vehicle or drugs were administered through the indwelling subcutaneous catheter.

Data Analysis

Only results derived from healthy rats with correctly positioned dialysis probes were included in the data analysis. Mean pre-drug baseline levels (time −90 min, −60 min, −30 min and 0) were designated as 100%. The net-AUC (area under the curve) was calculated from the absolute net increase for a 180-min period (six samples) after subtracting each pre-drug baseline value. The %net-AUC is the net-AUC value expressed as a percentage of each baseline AUC value. Repeated measure ANOVA followed by Fisher's protected least significant difference post-hoc pairwise comparison procedure was used to determine group differences (StatView 4.5 for the Macintosh). A $p < .05$ was considered significant in this study. All results are reported as mean ± SE

RESULTS

Basal concentrations of DA in the dialysate (fmol/20 μl) were 2.40 ± 0.11 (n = 83) in the mPFC and 21.3 ± 1.0 (n = 82) in the NAC, respectively. There were no significant differences in basal DA concentrations in the mPFC and NAC between treatment groups.

SR46349-B (10 mg/kg, but not 1 or 3 mg/kg) increased DA release in the mPFC, but had no effect on that in the NAC at all doses tested (Figure 1, panels A and B). SR46349-B (1 and 3 mg/kg) dose-dependently potentiated the haloperidol (0.1 mg/kg)-induced DA release in the mPFC and NAC, although only the effect of the 3 mg/kg dose reached significance in the NAC (Figure 2, panels A and B). SR46349-B (1 mg/kg) signif-

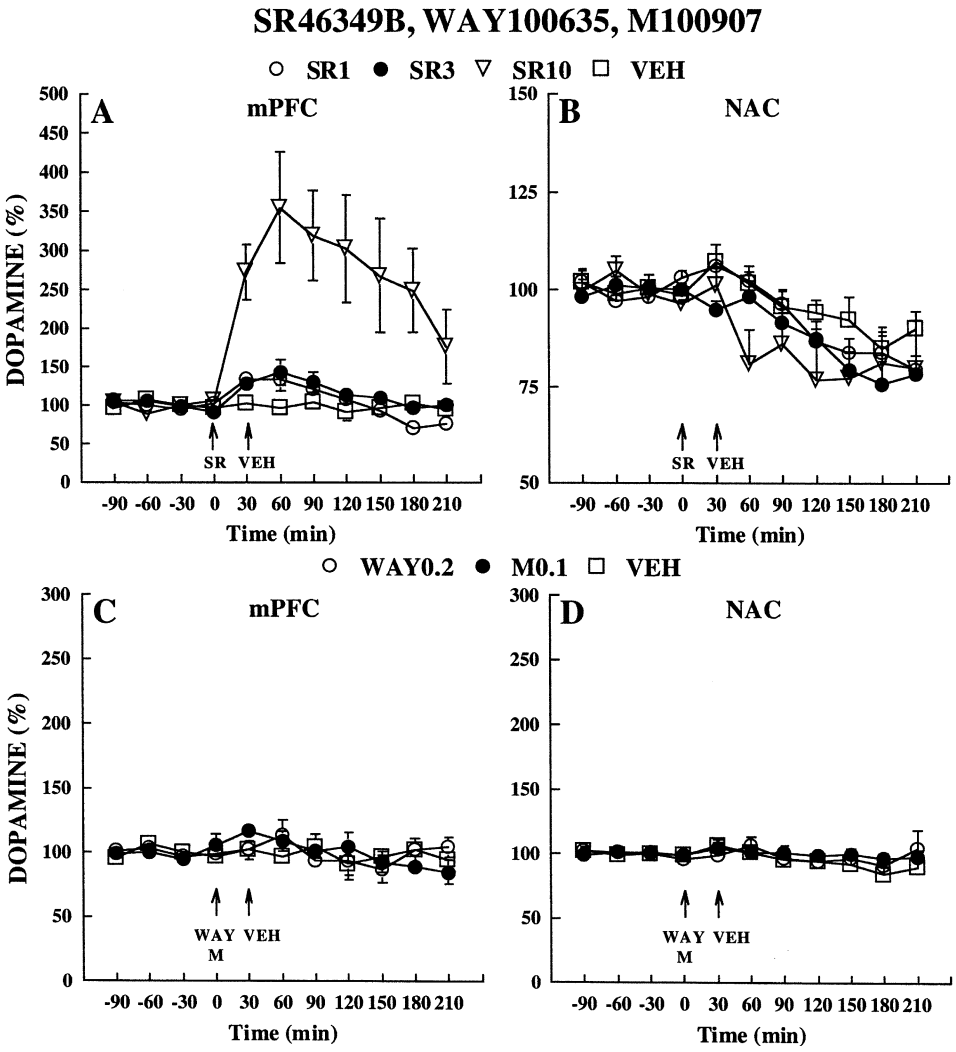

Figure 1. The time-course effect of SR46349-B (SR) and M100907 (M), selective 5-HT$_{2A}$ receptor antagonists, and WAY100635 (WAY), a selective 5-HT$_{1A}$ receptor antagonist, followed by vehicle (VEH). A. SR markedly increased DA release in the mPFC at 10 mg/kg (▽, $F_{1,9}$ = 12.74, p = .006), but not at 1 mg/kg (○, $F_{1,11}$ = 0.63, p = .44) or 3 mg/kg (●, $F_{1,9}$ = 4.65, p = .060), compared with VEH (□). However, there was a significant difference ($F_{1,9}$ = 6.56, p = .031) between the effect of 3 mg/kg and that of VEH when compared at 30, 60, 90 and 120 min following SR. B. SR (1, 3, and 10 mg/kg) had no significant effect on DA release in the NAC (○, $F_{1,11}$ = 0.64, p = .44; ●, $F_{1,10}$ = 3.10, p = .11; or ▽, $F_{1,9}$ = 2.38, p = .16, respectively), compared with VEH (□). C, D. WAY (0.2 mg/kg, ○) or M (0.1 mg/kg, ●) had no significant effect on DA release in the mPFC and NAC, compared with VEH (□). n = 4–7.

icantly potentiated high dose haloperidol (1 mg/kg)-induced DA release in the mPFC and NAC (Figure 2, panels C and D). The potentiation by SR46349-B (1 mg/kg) of haloperidol (0.1 mg/kg)-induced DA release in the mPFC was completely abolished by WAY100635 (0.2 mg/kg) (Figure 3, panel A). However, WAY100635 (0.2 mg/kg) did not significantly affect the potentiation by SR46349-B (1 mg/kg) of haloperidol (0.1 mg/kg)-induced DA release in the NAC (Figure 3, panel B). Similarly, M100907 (0.1 mg/kg) potentiated haloperidol (0.1 mg/kg)-induced DA release in the mPFC. This potentiation by M100907 was completely abolished and further significantly decreased below vehicle controls by WAY100635 (0.2 mg/kg) (Figure 3, panel C). WAY100635 (0.2 mg/kg) had no effect on the ability of M100907 (0.1 mg/kg) to inhibit haloperidol (0.1 mg/kg)-induced DA release in the NAC (Figure 3, panel D). Analysis of the %net-AUC of the above-mentioned effects on DA release clearly showed the dose-relationship and regional differences in the mPFC and NAC (Figure 4).

Interestingly, similar to the effect of SR46349-R, high dose M100907 (3 mg/kg) potentiated the ability of high dose haloperidol (1 mg/kg) to increase DA release in the mPFC and NAC (Figure 5). M100907 (3 mg/kg) alone had no significant effect on DA release in either region.

DISCUSSION

The major findings in this study are that SR46349-B by itself increased basal DA release in the mPFC, but not the NAC, and that SR46349-B potentiated haloperidol-induced DA release in the mPFC and NAC. The potentiation by SR46349-B and M100907 of haloperidol-induced DA release in the mPFC was completely abolished by the 5-HT$_{1A}$ receptor antagonist WAY100635.

Effects on Basal DA Release

High dose (10 mg/kg), but not low dose (1 or 3 mg/kg) SR46349-B significantly increased DA release in the

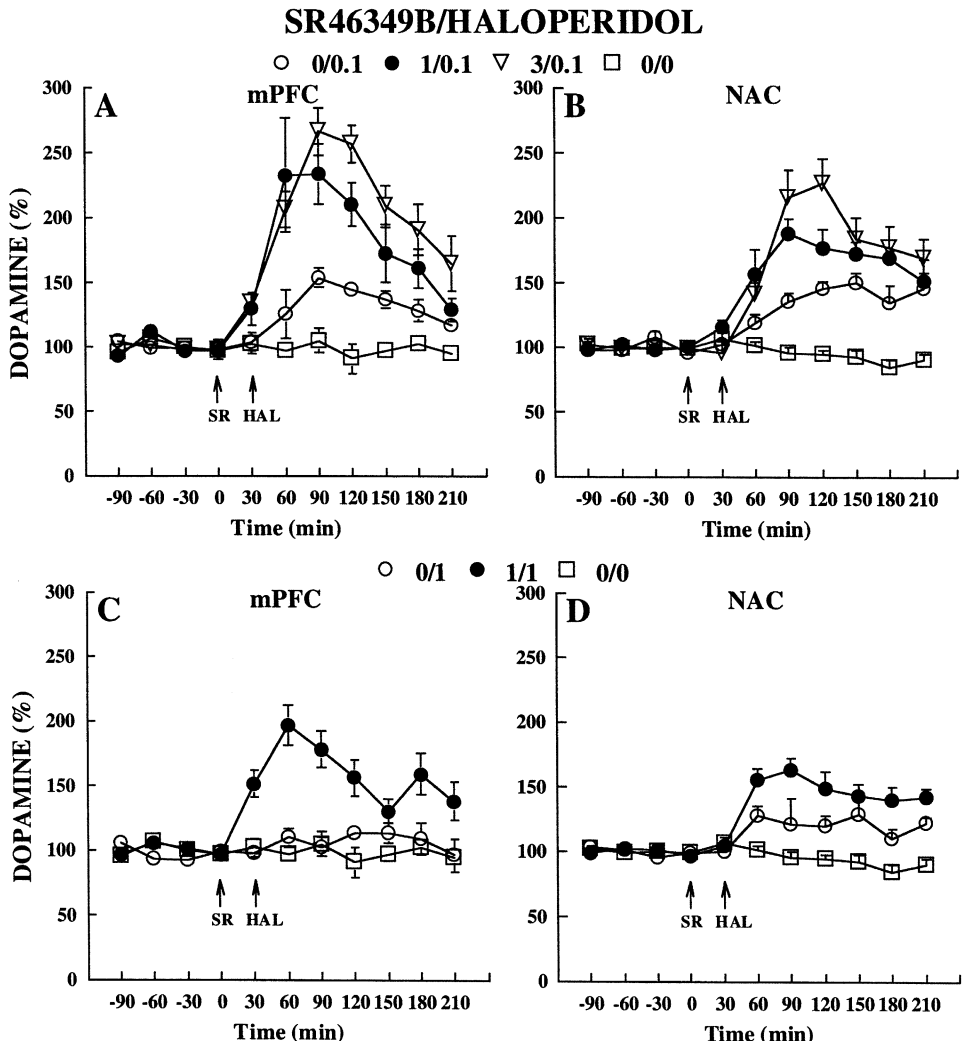

Figure 2. The time-course effect of SR46349-B (SR), a selective 5-HT_{2A} receptor antagonist, haloperidol (HAL) and their combination. A, B. HAL (0.1 mg/kg, ○) significantly increased DA release in the mPFC ($F_{1,11} = 29.37$, $p < .001$) and NAC ($F_{1,9} = 48.46$, $p < .001$), respectively, compared with vehicle controls (VEH, □). SR (1 mg/kg, ●, and 3 mg/kg, ▽), given 30 min prior to HAL, significantly increased the ability of HAL (0.1 mg/kg) to increase DA release in the mPFC ($F_{1,12} = 13.19$, $p = .003$; and $F_{1,13} = 54.82$, $p < .001$, respectively) and NAC (3 mg/kg, $F_{1,9} = 15.11$, $p = .004$; but not 1 mg/kg, $F_{1,10}$, $p = .067$), respectively, compared with the effect of HAL itself (○). C, D. HAL (1 mg/kg, ○) significantly increased DA release in the NAC ($F_{1,9} = 9.72$, $p = .012$), but not mPFC ($F_{1,10} = 1.44$, $p = .26$), compared VEH (□). SR (1 mg/kg, ●), given 30 min prior to HAL, significantly increased the ability of HAL (1 mg/kg) to increase DA release in the mPFC ($F_{1,8} = 32.79$, $p < .001$) and NAC ($F_{1,9} = 5.22$, $p = .048$), respectively, compared with the effect of HAL itself (○). n = 4–8.

mPFC, similar to the effect of ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, which is also a DA uptake inhibitor (Ruiu et al. 2000), at high (3 and 5 mg/kg) but not low doses (1, 1.5, and 2 mg/kg) (Nomikos et al. 1994; Pehek 1996). These effects of high dose SR46349-B and ritanserin to increase cortical DA release may be due mostly to 5-HT_{2C} receptor blockade since SR46349-B has moderate in vitro affinity for 5-HT_{2C} receptors (IC_{50} = 120 nM in pig cortex), compared with 5-HT_{2A} receptors (IC_{50} = 5.8 nM in rat cortex) (Rinaldi-Carmona et al. 1992), and the selective 5-HT_{2C} receptor antagonist SB242084 has been reported to increase DA release in the mPFC (Millan et al. 1998) and NAC (Di Matteo et al. 1999; Gobert et al. 2000). The lack of an effect of SR46349-B (1, 3, and 10 mg/kg) on DA release in the NAC in the present study is consistent with the data of De Deurwaerdère and Spampinato (1999) and Di Giovanni et al. (1999, 2000). The difference between SR46349-B and SB242084 may be due to the potent 5-HT_{2A} receptor antagonism of SR46349-B. On the other hand, M100907, a selective 5-HT_{2A} receptor antagonist (Ki = 0.36 nM for 5-HT_{2A}, and 105 nM for 5-HT_{2C} receptors, respectively; Carr et al. 1991), has been reported not to affect DA release in either the mPFC or the NAC

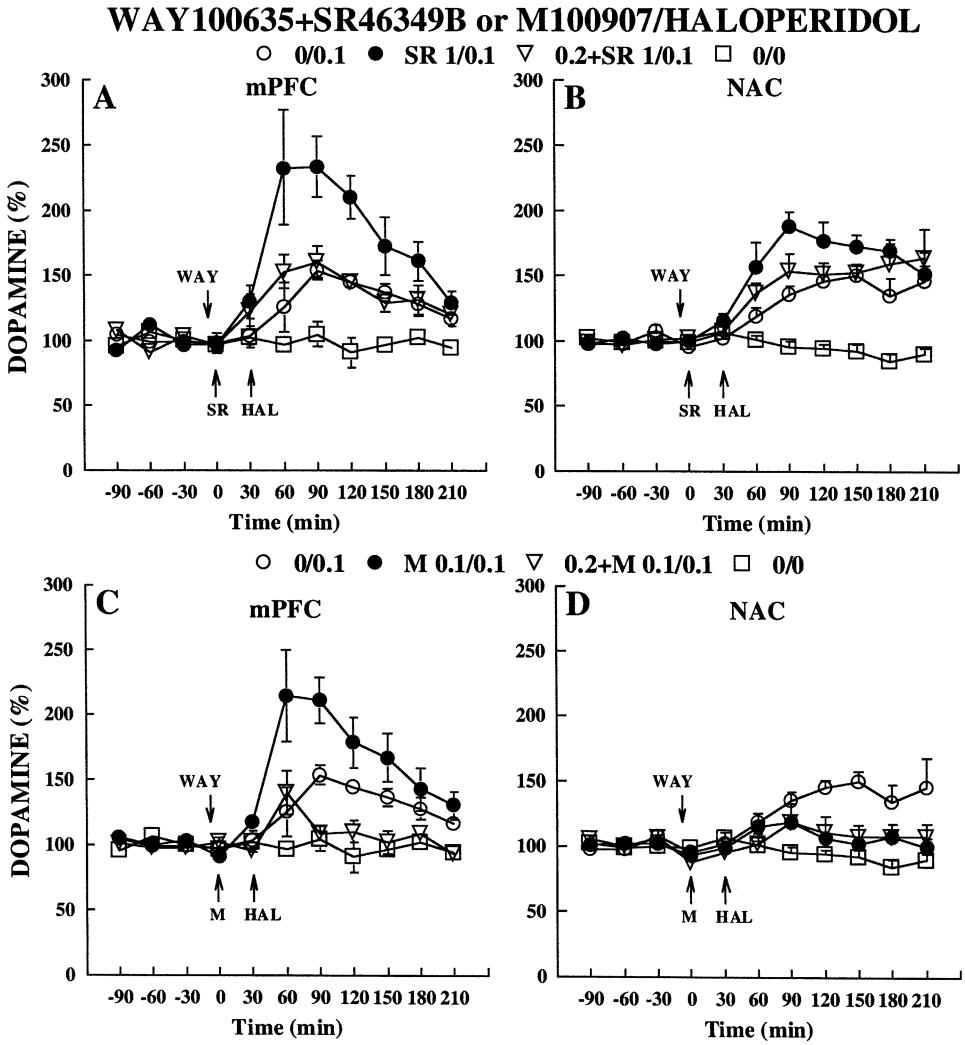

Figure 3. The time-course effect of WAY100635 (WAY), a selective 5-HT_{1A} receptor antagonist, SR46349-B (SR) and M100907 (M), selective 5-HT_{2A} receptor antagonists, haloperidol (HAL) and their combination. A, B. WAY (0.2 mg/kg), given 5 min prior to SR, abolished HAL (0.1 mg/kg, ○)-induced DA release enhanced by SR (1 mg/kg) in the mPFC (▽, $F_{1,10} = 7.83$, $p = .019$), but not NAC (▽, $F_{1,11} = 1.71$, $p = .22$), compared with the effect of a combination of SR and HAL (●). C, D. M (0.1 mg/kg), given 30 min prior to HAL, increased the ability of HAL (0.1 mg/kg) to increase DA release in the mPFC (●, $F_{1,12} = 13.76$, $p = .003$), but inhibited that in the NAC (●, $F_{1,10} = 33.42$, $p < .001$), compared with the effect of HAL itself (○). WAY (0.2 mg/kg), given 5 min prior to M, abolished HAL (0.1 mg/kg)-induced DA release enhanced by M (0.1 mg/kg) in the mPFC (▽, $F_{1,10} = 25.64$, $p < .001$), compared with the effect of a combination of M and HAL (●), and further decreased DA release ($F_{1,10} = 9.78$, $p = .011$), compared with the effect of HAL alone (○). WAY (0.2 mg/kg) had no effect on HAL (0.1 mg/kg)-induced DA release inhibited by M (0.1 mg/kg) in the NAC (▽), compared with the effect of a combination of SR and HAL (●). n = 4–8.

(present data; Gobert and Millan 1999; Ichikawa and Meltzer 2000; Rollema et al. 2000; Zhang et al. 2000; Ichikawa et al. 2001a,b; Pehek et al. 2001; Westerink et al. 2001; Liégeois et al. 2002). Thus, it is possible that the difference between SR46349-B and M100907 in their abilities to affect basal as well as haloperidol-induced DA release in the mPFC and NAC is due, at least in part, to blockade of 5-HT_{2C} receptors by SR46349-B, but not by M100907.

Effects on Haloperidol-induced DA Release in the mPFC

We have reported that low (0.1 m g/kg), but not high dose (1 mg/kg), haloperidol significantly increased DA release in the mPFC, while both doses significantly increased DA release in the NAC (Liégeois et al. 2002), most likely due to D_2 receptor blockade. The evidence that both SR46349-B (1 and 3 mg/kg) and M100907 (0.1 mg/kg) potentiated low dose haloperidol (0.1 mg/kg)-induced

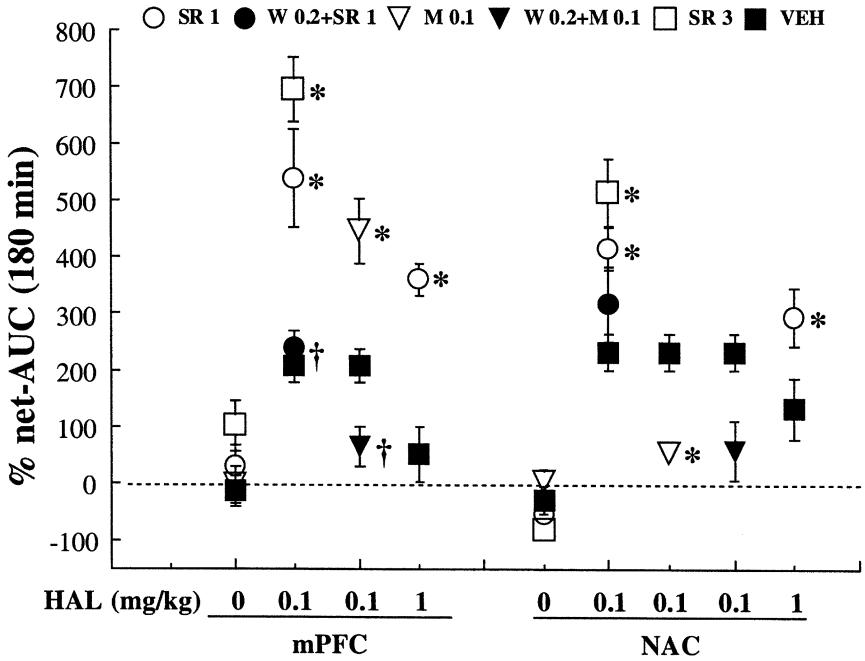

Figure 4. Analysis of the %net-AUC (area under the curve) provides direct comparison of dose related effects of haloperidol (HAL, 0.1 and 1 mg/kg) in combination with SR46349-B (SR, 1, ○; and 3 mg/kg, □), M100907 (M, 0.1 mg/kg, ▽) and WAY100635 (W, 0.2 mg/kg, ▼). SR (1 and 3 mg/kg), a selective 5-HT_{2A} receptor antagonist, potentiated HAL (0.1 and 1 mg/kg)-induced DA release in the mPFC and NAC. M (0.1 mg/kg), a selective 5-HT_{2A} receptor antagonist, potentiated HAL (0.1 mg/kg)-induced DA release in the mPFC, but inhibited that in the NAC. WAY (0.2 mg/kg) completely abolished the potentiation effect of SR (1 mg/kg) and M (0.1 mg/kg) on HAL (0.1 mg/kg)-induced DA release in the mPFC. WAY (0.2 mg/kg) did not affect the effect of either SR (1 mg/kg) or M (0.1 mg/kg) on HAL (0.1 mg/kg)-induced DA release in the NAC. * indicates significant difference from the effect of HAL alone (■). † indicates significant difference from the effect of a combination of HAL with SR or M. n = 4–8.

DA release in the mPFC suggests that the potentiation may be due to the combined effects of 5-HT_{2A} and D_2 receptor blockade (Ichikawa et al. 2001a,b). The nearly identical potentiation by 0.1 mg/kg M100907 and 1 mg/kg SR36349-B of 0.1 mg/kg haloperidol-induced DA release in the mPFC indicates that 1 mg/kg SR46349-B may be equivalent to 0.1 mg/kg M100907 as a 5-HT_{2A} receptor antagonist in vivo. Reversal by WAY100635 (0.2 mg/kg), a selective 5-HT_{1A} receptor antagonist, of the potentiation by SR46349-B (1 mg/kg) and M100907 (0.1 mg/kg) supports our hypothesis that facilitation of 5-HT_{1A} receptor stimulation is essential to the combined blockade of 5-HT_{2A} and D_2 receptor to increase DA release in the mPFC (Ichikawa et al. 2001a). Interestingly, WAY100635 (0.2 mg/kg) significantly decreased the effect of M100907 (0.1 mg/kg) plus haloperidol (0.1 mg/kg) on DA release in the mPFC below the effect of haloperidol alone. However, it is unlikely that the effect of low dose haloperidol by itself to increase DA release in the mPFC is due to 5-HT_{1A} receptor stimulation because WAY100635 did not further decrease the effect of haloperidol alone on DA release in the mPFC, when combined with SR46349-B.

It is noteworthy that SR46349-B (1 mg/kg) also potentiated high dose (1 mg/kg) haloperidol-induced DA release in the mPFC, which contrasts the lack of effect of M100907 (0.1 mg/kg) to do so (Liégeois et al. 2002). Although the mechanism by which haloperidol (0.01–1 mg/kg) produces an inverted U-shaped increase in DA release in the mPFC is unknown (Liégeois et al. 2002), haloperidol (1 mg/kg) by itself had no effect on DA release in the mPFC. 5-HT_{2C} receptor antagonism may be relevant to the ability of SR46349-B (1 mg/kg), but not M100907 (Liégeois et al. 2002), to potentiate high dose (1 mg/kg) haloperidol-induced DA release in the mPFC. However, it should be noted that many, but not all, typical APDs, including haloperidol, as well as atypical APDs such as clozapine, are 5-HT_{2C} receptor antagonists (Roth et al. 1992), and that Ro 60-0175 (3 mg/kg), a selective 5-HT_{2C} receptor agonist, did not affect the ability of clozapine (20 mg/kg) to increase DA release in the mPFC (Ichikawa et al. 2001b). These results suggest that 5-HT_{2C} receptor antagonism may not solely contribute to the ability of clozapine and the related 5-HT_{2C} receptor antagonist APDs to increase DA release in the mPFC. Therefore, the precise mechanism by which SR46349-B potentiates high dose (1 mg/kg) haloperidol-induced DA release in the mPFC remains to be determined.

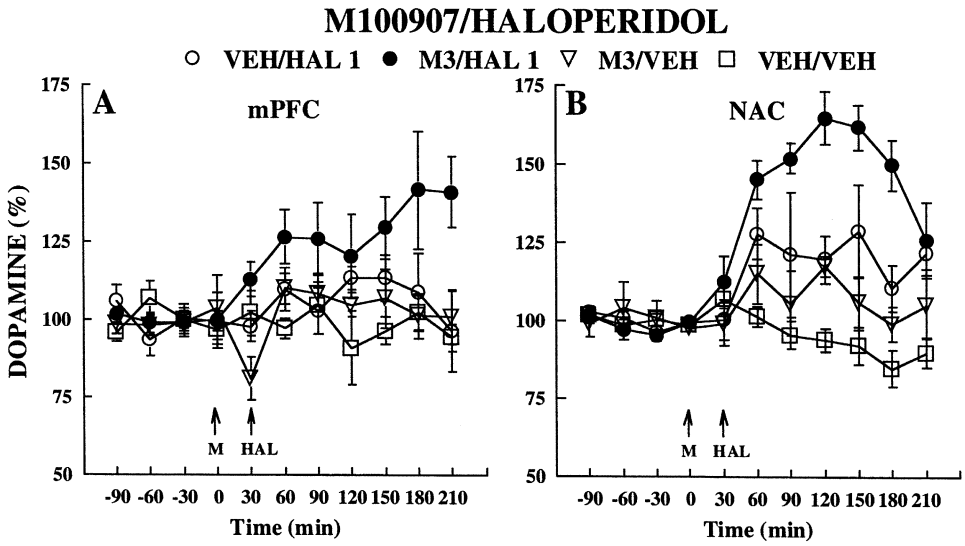

Figure 5. The time-course effect of M100907 (M), a selective 5-HT$_{2A}$ receptor antagonist, haloperidol (HAL) and their combination. A, B. High dose M (3 mg/kg), given 30 min prior to HAL, increased the ability of high dose HAL (1 mg/kg) to increase DA release in the mPFC (●, $F_{1,10} = 7.61$, $p = .020$), compared with vehicle controls (VEH, □), although this combination did not significantly differ from the ability of HAL itself ($F_{1,10} = 3.26$, $p = .10$) or M alone ($F_{1,10} = 4.83$, $p = .053$), respectively. The same combination of M and HAL produced a significantly greater increase in DA release in the NAC, compared with the affect of HAL alone (●, $F_{1,9} = 9.04$, $p = .015$). M (3 mg/kg) by itself had no significant effects on DA release in the mPFC and NAC, compared with vehicle controls. n = 4–6.

Effects on Haloperidol-induced DA Release in the NAC

SR46349-B had an effect opposite to that of M100907 (0.1 mg/kg) on haloperidol-induced DA release in the NAC. SR46349-B (1 mg/kg) together with both low and high dose haloperidol (0.1 and 1 mg/kg) produced significantly greater increases in DA release in the NAC, compared with the effect of haloperidol alone. By sharp contrast, M100907 (0.1 mg/kg) inhibited both 0.1 and 1 mg/kg haloperidol-induced DA release in the NAC (present data; Liégeois et al. 2002). These differences may be attributed to the 5-HT$_{2C}$ receptor antagonist property of SR46349-B, compared with selective 5-HT$_{2A}$ receptor antagonism by M100907, since ritanserin, a mixed 5-HT$_{2A/2C}$ receptor antagonist, potentiated the D$_{2/3}$ receptor antagonist raclopride-induced DA release in the mPFC and NAC, but not STR (Andersson et al. 1995). Ritanserin has almost equivalent affinities for 5-HT$_{2A}$ (Ki = 3.8 nM) and 5-HT$_{2C}$ receptors (2.7 nM) (Roth et al. 1992), whereas M100907 is much more selective for 5-HT$_{2A}$ receptors (Carr et al. 1991), as mentioned above. Ritanserin (1.25 mg/kg) and SR46349-B (0.5 mg/kg) have been reported to attenuate low dose (0.01 and 0.1 mg/kg), but not high dose (1 mg/kg), haloperidol-induced DA release in the STR, whereas SB206553, a 5-HT$_{2B/2C}$ receptor antagonist, potentiated haloperidol (0.01, but not 1, mg/kg)-induced striatal DA release (Spampinato et al. 1998; Lucas et al. 2000). Interestingly, De Deurwaerdère and Spampinato (1999) also reported that SR46349-B (0.5 mg/kg) and ritanserin (0.63 mg/kg) reversed an increase in DA release in the NAC produced by the electrical stimulation of the dorsal raphe nuclei. Thus, it appears that low dose SR46349-B (0.5 mg/kg) may be more selective for 5-HT$_{2A}$ receptors, whereas high dose SR46349-B (1, 3, and 10 mg/kg), as in the present study, may have appreciable 5-HT$_{2C}$ receptor antagonist properties, in vivo, as well as 5-HT$_{2A}$ receptor antagonism. The discrepancy between the present data in the NAC and the results of others in the STR (Spampinato et al. 1998; Lucas et al. 2000) may also be due, in part, to the difference in the distribution of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. 5-HT$_{2A}$ receptors are sparsely distributed in the NAC compared with the STR (Appel et al. 1990; Morilak et al. 1993), whereas 5-HT$_{2C}$ receptors are widely distributed in the brain (Barnes and Sharp 1999). Differences in the extent of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor antagonism by drugs are, therefore, important because of their differential effects on DA release in various terminal regions of the DA system.

In this regard, high dose M100907 (3 mg/kg) also potentiated high dose haloperidol (1 mg/kg)-induced DA release in the mPFC and NAC (Figure 5), whereas 0.1 mg/kg M100907 failed to affect 1 mg/kg haloperidol-induced DA release in the mPFC, but inhibited that in the NAC (present data; Liégeois et al. 2002). These results may support our hypothesis that SR46349-B (1 mg/kg) potentiated the ability of haloperidol to in-

crease DA release in the mPFC and NAC, presumably in large part, due to 5-HT_{2C} receptor antagonism or, more likely, mixed 5-$HT_{2A/2C}$ receptor antagonism, since high dose M100907 would be expected to have also 5-HT_{2C} receptor antagonist property (Ki = 88 nM) despite its high selectivity for the 5-HT_{2A} receptor (Ki = 0.85 nM, Kehne et al. 1996). Furthermore, it should be noted that an inverse agonist activity of M100907 and some of typical and atypical APDs has been suggested to be important to their antipsychotic actions (Rauser et al. 2001; Weiner et al. 2001). M100907 also has virtually identical affinity for the sigma receptor (Ki = 87 nM, Kehne et al. 1996). However, this seems to be unlikely to contribute to the effect of high dose M100907 to potentiate haloperidol-induced DA release in the mPFC and NAC, because haloperidol is a potent sigma receptor antagonist (Ki = 1.1 nM, Schotte et al. 1996).

We have reported that R(+)-8-OH-DPAT (0.05, mg/kg), a selective 5-HT_{1A} receptor agonist, which by itself decreased basal DA release in the NAC only at high doses (0.2 mg/kg, but not 0.1 or 0.05 mg/kg), had the following effects: (1) it inhibited the clozapine (20 mg/kg) and low dose risperidone (0.01 and 0.03 mg/kg)-induced DA release in the NAC, an effect reversed by WAY100635; and (2) potentiated the ability of low dose S(-)-sulpiride (1 and 3 mg/kg), a $D_{2/3}$ receptor antagonist, to increase DA release in the NAC; although (3) it had no effect on the ability of high dose S(-)-sulpiride (10 and 25 mg/kg) and risperidone (0.1 or 1, mg/kg), as well as all doses of haloperidol (0.01, 0.03, 0.1 and 1 mg/kg), to increase DA release in the NAC (Ichikawa and Meltzer 1999b, 2000). We also reported no effect of M100907 (1 mg/kg) on the ability of R(+)-8-OH-DPAT (0.2 mg/kg) to decrease DA release in the NAC (Ichikawa and Meltzer 2000). These results suggest that the combination of potent 5-HT_{2A} and weak D_2 receptor antagonism produced by atypical APDs may facilitate the ability of 5-HT_{1A} receptor stimulation to decrease DA release in the NAC. However, 5-HT_{1A} receptor stimulation is unlikely to be involved in either the potentiation by SR46349-B or the inhibition by M100907 of haloperidol-induced DA release in the NAC because WAY100635 had no significant effect on either of the potentiation or inhibition, although further studies may be warranted because of the slight but non-significant effect. Thus, combined blockade of 5-HT_{2A} and/or 5-HT_{2C}, and D_2 receptors may modulate DA release in the NAC, via processes independent of 5-HT_{1A} receptor stimulation, although it may be affected by additional 5-HT_{1A} receptor stimulation. Alternatively, it is further suggested that the ability of D_2 receptor blockade to increase DA release in the NAC, compared with the mPFC, may be directly affected by 5-HT_{2A} and 5-HT_{2C} receptors.

There is evidence that some 5-HT_{2A} receptor antagonists can decrease the radiolabeled drug binding to D_2 receptors. For example, ketanserin, a 5-HT_{2A} receptor antagonist, has recently been reported to dose-dependently decrease striatal binding of [^{11}C]raclopride, a $D_{2/3}$ receptor antagonist, in the monkey, as measured by positron emission tomography (PET) scanning (Tsukada et al. 1999). The ketanserin-induced reduction of [^{11}C]raclopride binding was not due to an increase in synaptic DA concentrations, a possible cause of decreased [^{11}C]raclopride binding (Seeman et al. 1989; Dewey et al. 1993) since ketanserin produces minimal increases in striatal DA release (Tsukada et al. 1999). Raclopride, by itself, has been reported not to affect the binding of [^{11}C]M100907 in any region of the post-mortem human brain (Hall et al. 2000). Thus, it is intriguing to hypothesize that, in the NAC, M100907 decreases the blockade of presynaptic D_2 autoreceptors by haloperidol, and that SR46349-B similarly increases the affinity of haloperidol for these D_2 autoreceptors due to 5-HT_{2C} receptor antagonism, with or without 5-HT_{2A} receptor antagonism, causing an increase and decrease, respectively, of DA release in that region.

Clinical Implications

The results reported here suggest that 5-HT_{2A} receptor blockade may be an useful method to augment actions of typical APDs as well as being a key component of the action of some atypical APDs. The typical APDs such as haloperidol have limited effects on negative and cognitive symptoms of schizophrenia, compared with the superior effect of atypical APDs such as clozapine, olanzapine, risperidone, quetiapine, ziprasidone, iloperidone, and melperone (Meltzer and McGurk 1999; see the introductory paragraphs of this article). Thus, it is proposed that the addition of 5-HT_{2A} receptor antagonism (a feature common to all of the atypical APDs listed above) to haloperidol, fluphenazine, or other typical APDs, which are themselves devoid of appreciable 5-HT_{2A} receptor antagonism, may achieve at least some of the benefits of the atypical APDs; for example, facilitation of dopaminergic transmission in the cortex (suggested to be reduced in schizophrenia) and attenuation of dopaminergic transmission in the mesolimbic system (suggested to be increased in schizophrenia) (Davis et al. 1991). Specifically, M100907 inhibition of haloperidol-induced DA release in the NAC and perhaps also the potentiation of DA release in the mPFC may be relevant to its ability to potentiate haloperidol-induced CAR (Hicks et al. 1999; Wadenberg et al. 2001). Mixed 5-$HT_{2A/2C}$ receptor antagonism may be useful for improving cognition and negative symptoms in schizophrenia when it is combined with high dose haloperidol because of increased cortical DA release, while producing more potent blockade of D_2 receptors to ameliorate psychosis. The role of 5-HT_{2C} receptor antagonism in antipsychotic action needs further clarification.

CONCLUSION

The 5-HT2A receptor antagonists SR46349-B and M100907 can potentiate the ability of the typical APD haloperidol to increase DA release in the mPFC, via a 5-HT1A receptor-dependent mechanism, as has been shown by the atypical APDs (Ichikawa et al. 2001a). This combination may produce some of clinically relevant effects of atypical APDs. SR46349-B differs from M100907, a more selective 5-HT2A receptor antagonist, probably due to its 5-HT2C receptor antagonist properties. This difference may explain the ability of SR46349-B and M100907 (0.1, but not 3, mg/kg) to respectively potentiate and inhibit haloperidol-induced DA release in the NAC, via 5-HT1A receptor-independent processes.

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