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Effect of antipsychotic drugs on extracellular serotonin levels in rat medial prefrontal cortex and nucleus accumbens

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Abstract

Amperozide, clozapine, olanzapine and risperidone are more potent serotonin (5-hydroxytryptamine, 5-HT)$_{2A}$ receptor antagonists than dopamine D_2-like receptor antagonists. Haloperidol and *S*(−)-sulpiride are potent or selective dopamine D_2-like receptor antagonists and lack 5-HT$_{2A}$ receptor antagonist properties. We studied the effect of these five proven antipsychotic drugs and one putative (amperozide) antipsychotic drug on extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens of awake, freely-moving rats, using in vivo microdialysis with dual probe implantation. Risperidone (1 mg/kg) and clozapine (20 mg/kg) significantly increased extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens, respectively. Amperozide (2 and 10 mg/kg) significantly increased extracellular 5-HT levels in both regions. Olanzapine (1 and 10 mg/kg), *S*(−)-sulpiride (10 and 25 mg/kg), haloperidol (0.1 and 1 mg/kg) and the selective 5-HT$_{2A}$ receptor antagonist MDL-100,907 (1 mg/kg) had no significant effect on extracellular 5-HT levels in either region. Thus, the ability to increase extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens by these antipsychotic drugs is not directly related to their affinity for 5-HT$_{2A}$ receptors since olanzapine and MDL-100,907 had no significant effect on extracellular 5-HT levels. A variety of mechanisms other than those involving 5-HT$_{2A}$ receptors, e.g., reuptake inhibition (amperozide) and blockade of α_2-adrenoceptors (clozapine), may contribute to the ability to increase extracellular 5-HT levels in the brain. The increase in extracellular 5-HT levels in the medial prefrontal cortex or nucleus accumbens following amperozide, clozapine, or risperidone administration may not be related to the effect on psychotic symptoms but could be related to effects on other types of psychopathology such as depression, negative symptoms, or cognition.

Keywords: Antipsychotic drug; MDL-100,907; 5-HT (5-hydroxytryptamine, serotonin); Cortex, medial prefrontal; Nucleus accumbens; Microdialysis, in vivo; (Rat)

1. Introduction

The ability of antipsychotic drugs to modulate serotonergic as well as dopaminergic function has been suggested to be important for their efficacy and side-effect profiles (Breier, 1995; Roth and Meltzer, 1995; Abi-Dargham et al., 1997). There has been extensive study of the effect of antipsychotic drugs on the medial prefrontal cortex and the nucleus accumbens because of the possible importance of both regions for cognition, negative or positive symptoms of schizophrenia (see Davis et al., 1991 for review). There has been relatively less study of the effect of these agents on the release of serotonin (5-hydroxytryptamine, 5-HT). It has been reported that the antipsychotic drugs, haloperidol (5 and 20 mg/kg) (Petty et al., 1994), risperidone (0.6 and 2 mg/kg) (Hertel et al., 1996, 1997a) and amperozide (10 mg/kg) (Hertel et al., 1997a) increase extracellular 5-HT levels in the medial prefrontal cortex while clozapine (5 mg/kg) has been reported to decrease extracellular 5-HT levels in the nucleus accumbens (Ferré and Artigas, 1995). These results indicate that antipsychotic drugs may affect the release of 5-HT as well as dopamine in the brain in diverse ways.

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The precise mechanism(s) by which antipsychotic drugs affect extracellular 5-HT levels in the brain and their clinical significance are not known. Stimulation of 5-HT_{1A} autoreceptors inhibits 5-HT release (Hjorth and Sharp, 1991) while blockade of 5-HT_{1A} autoreceptors causes an increase (Assié and Koek, 1996a; Matos et al., 1996) or no change (Assié and Koek, 1996b) in 5-HT release. However, most antipsychotic drugs with the exception of ziprasidone (Seeger et al., 1995) and quetiapine (Leysen et al., 1993) have minimal affinity for 5-HT_{1A} receptors relative to 5-HT_{2A} receptors (Mason and Reynolds, 1992; Leysen et al., 1993; Schotte et al., 1996) while most atypical antipsychotic drugs, including clozapine, risperidone and olanzapine, have high affinity for 5-HT_{2A} receptors (Meltzer et al., 1989; Leysen et al., 1993; Schotte et al., 1996). There is evidence that 5-HT_{2A} receptors may affect extracellular 5-HT levels in the brain: (1) the 5-$HT_{2A/2C}$ receptor agonist (±)-DOI (1-(2,5-dimethoxy-4-iodophenyl)-aminopropane) hydrochloride decreases extracellular 5-HT levels in the frontal cortex (Wright et al., 1990); and (2) ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, has been reported to increase extracellular 5-HT levels in the nucleus accumbens of the rat (Devaud et al., 1992). Based on these findings, we postulated that all 5-HT_{2A}/dopamine D_2-like receptor antagonist antipsychotic drugs, e.g., olanzapine (Beasley et al., 1996) or risperidone (Chouinard et al., 1994), would be expected to increase extracellular 5-HT levels while selective dopamine D_2-like receptor antagonists with no appreciable affinity for 5-HT_{2A} receptors such as raclopride or *S*(−)-sulpiride may have no effect on extracellular 5-HT levels (Ferré and Artigas, 1995; Chen and Reith, 1995). The effect of antipsychotic drugs on extracellular 5-HT levels may contribute to the difference in pharmacological and, possibly, clinical effects between antipsychotic drugs like clozapine with 5-HT_{2A}/dopamine D_2-like receptor antagonist activity and selective dopamine D_2-like receptor antagonists like haloperidol and *S*(−)-sulpiride.

The present study was designed to test the hypothesis that antipsychotic drugs of the 5-HT_{2A}/dopamine D_2 receptor antagonist type modulate extracellular 5-HT levels, an effect mediated by the blockade of 5-HT_{2A} receptors. Six antipsychotic drugs and MDL-100,907, a selective 5-HT_{2A} receptor antagonist with numerous similarities to clozapine in preclinical behavioral profiles (Sorensen et al., 1993; Kehne et al., 1996), were chosen on the basis of the pK_i values for rat cortical 5-HT_{2A} and striatal dopamine D_2 receptors obtained from published sources.

2. Materials and methods

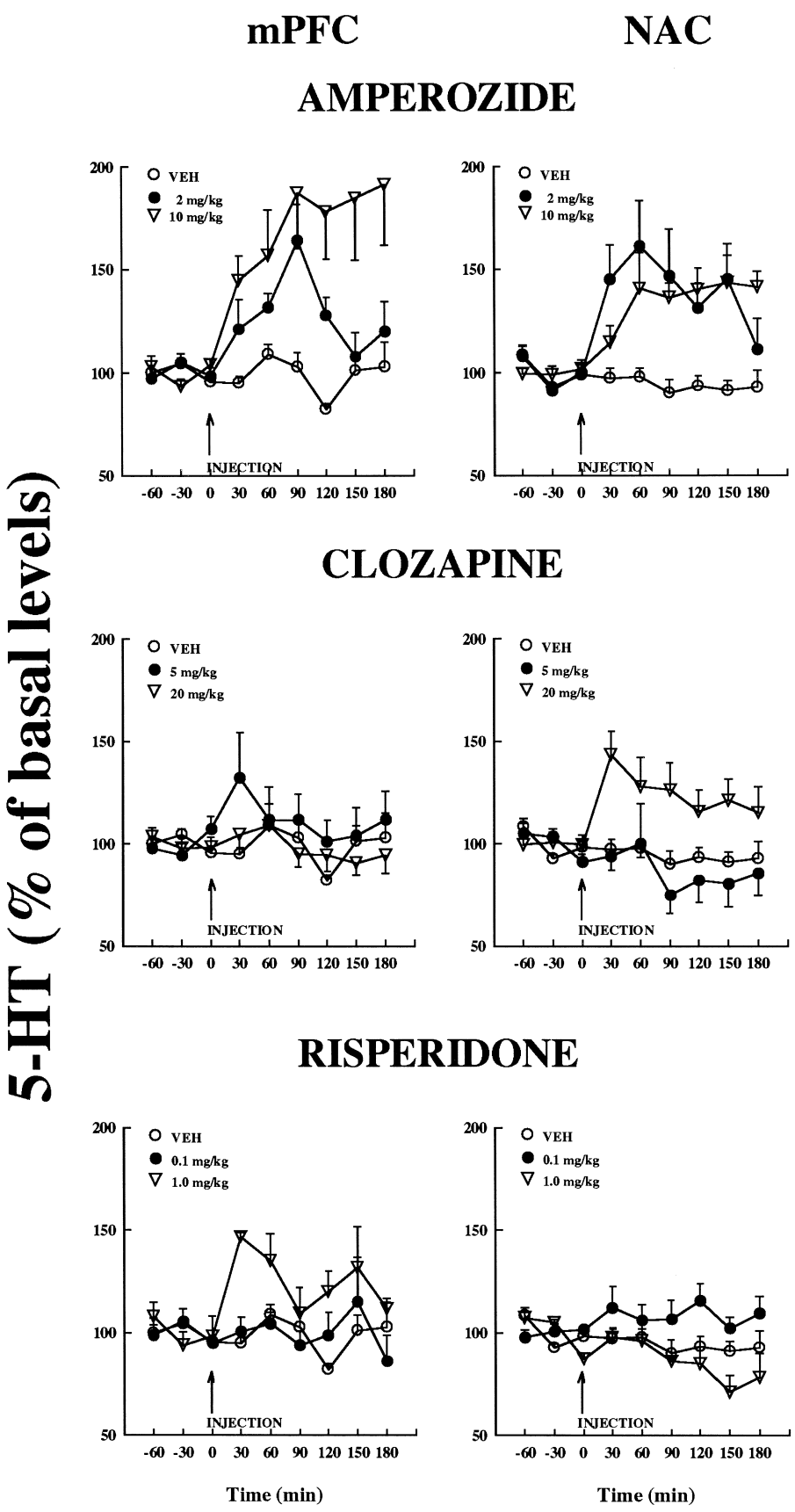
2.1. Animals

Male Sprague–Dawley albino rats (Zivic-Miller) weighing 250–300 g were used throughout the study. Rats were housed two or three per cage and maintained on a 12-h light/dark cycle and under constant temperature at 22°C, with ad libitum access to food and water.

2.2. Surgery and microdialysis

Rats were anesthetized with a combination of xylazine (6 mg/kg, i.p., Rompun®) and ketamine hydrochloride (70 mg/kg, i.p., Ketaset®) and mounted in a stereotaxic frame (Stoetling). Two stainless steel guide cannulas (21-gauge) with a dummy probe were placed and fixed with cranioplastic cement onto the cortex dorsal both to the medial prefrontal cortex and the nucleus accumbens (dual probe implantation). Stereotaxic coordinates of each probe when implanted were A + 3.2, L + 0.8 (10° inclination), V − 5.5 mm for the medial prefrontal cortex and A + 2.0, L + 1.7, V − 7.5 mm for the nucleus accumbens, respectively, relative to bregma; incision bar level: −3.0 mm, according to the atlas of Paxinos and Watson (1986). Three to five days following cannulation, the dialysis probes (2 mm in length of membrane, polyacrylonitrile/sodium methalylsulfonate polymer, 310 μm o.d., 220 μm i.d., AN69 HF, Hospal) were implanted into the medial prefrontal cortex and the nucleus accumbens under slight anesthesia with methoxyflurane (Metofane®). Dialysis probes were always implanted above or on the medial side of the anterior limb of the anterior commissure, a location which may be considered the shell of the nucleus accumbens. The probe was perfused with modified Dulbecco's phosphate-buffered saline including Ca^{2+} (NaCl 138 mM, Na_2HPO_4 8.1 mM, KCl 2.7 mM, KH_2PO_4 1.5 mM, MgCl 0.5 mM, $CaCl_2$ 1.2 mM, pH = 7.4) at 0.2 μl/min through the night to exclude blood-delivered 5-HT which can appear in the dialysate even 6 h after probe implantation (Kalén et al., 1988). After the overnight perfusion for approximately 15 h, the perfusion flow rate was increased to 0.4 μl/min and 1 h later, dialysate samples were collected every 30 min. After baseline concentrations in the dialysate became stable,

Fig. 1. Time-dependent effect of amperozide (○: vehicle, ●: 2 and ▽: 10 mg/kg, s.c.) (top), clozapine (○: vehicle, ●: 5 and ▽: 20 mg/kg, s.c.) (middle) and risperidone (○: vehicle, ●: 0.1 and ▽: 1.0 mg/kg, s.c.) (bottom) on extracellular 5-HT levels in the medial prefrontal cortex (mPFC, left) and the nucleus accumbens (NAC, right). The arrow indicates the drug injection time. Data are means ± S.E.M. ($N = 5–7$ for each treatment group) of corresponding time points, expressed as percentages of the pre-drug basal levels. Clozapine (▽: 20 mg/kg) and risperidone (1.0 mg/kg) produced significant increases in extracellular 5-HT levels in the NAC and the mPFC, respectively. Amperozide (●: 2 and ▽: 10 mg/kg) significantly increased extracellular 5-HT levels in both the mPFC and the NAC.


mPFC
NAC
AMPEROZIDE
CLOZAPINE
RISPERIDONE
5-HT (% of basal levels)
VEH
2 mg/kg
10 mg/kg
5 mg/kg
20 mg/kg
0.1 mg/kg
1.0 mg/kg
INJECTION
200
150
100
50
-60 -30 0 30 60 90 120 150 180
Time (min)

such that the percentage standard error (S.E.M.) of the three consecutive 5-HT values in the dialysate differed by less than 10% of the mean values, each drug or vehicle was administered subcutaneously (s.c.) to rats. The effect of the drug was monitored for another 180 min. The location of the dialysis probe was verified by macroscopic examination after completion of each experiment.

The procedures applied in this study were in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee (IAUAC) of Case Western Reserve University in Cleveland, OH, where we completed this study.

2.3. Biochemical assay

Concentrations of 5-HT in dialysate samples were simultaneously determined by high-performance liquid chromatography with electrochemical detection (HPLC–ECD) as previously described (Kuroki et al., 1996). The 5-HT was separated on a reversed-phase column (BDS Hypersil C18, 1.0 × 100 mm, 3 μm particle size, Keystone Scientific). The composition of the mobile phase was 50 mM NaH_2PO_4 (pH = 6.0), 20% (v/v) methanol, 8% (v/v) acetonitrile, 450 mg/l sodium dodecyl sulfate, 1 mM Na_2EDTA, 10 mM NaCl and 500 μl/l triethylamine. An electrochemical detection controller (LC-4C, BAS) with a unijet amperometric detector cell (MF-9080, BAS) set at +550–580 mV vs. a Ag/AgCl reference electrode was used to detect 5-HT. The column and detector cell were placed in a column oven (831 temperature regulator, Gilson) at 28–35°C. The data were analyzed for 5-HT with an integrator (HP 3396 Series II, Hewlett-Packard). The detection limit was 0.2 fmol for 5-HT at a 3:1 signal-to-noise ratio. All reagents used for HPLC–ECD were purchased from Fisher Scientific and Sigma.

2.4. Drugs

Amperozide–HCl (Pharmacia LEO Therapeutics) was dissolved in deionized water. Clozapine–HCl (Sandoz), risperidone (Janssen), olanzapine (Eli Lilly), haloperidol (McNeil), and *S*(−)-sulpiride (Research Biochemical) were dissolved in 0.1 M tartaric acid, respectively. The MDL-100,907 free base (Marion Merrell Dow) was dissolved in deionized water. Vehicle (0.1 M tartaric acid) or drugs in a volume of 1.0 ml/kg were administered subcutaneously (s.c.) to randomly assigned rats.

2.5. Data analysis

All data were statistically evaluated by using Super-ANOVA® (Abacus Concepts) and SPSS (SPSS). Data on basal extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens in various treatment groups were subjected to one-way analysis of variance (ANOVA). The time-dependent effects of drugs were analyzed by repeated measures of ANOVA followed by the Fisher's PLSD (protected least significant difference) post-hoc pairwise comparison procedures. A probability (P) of less than 0.05 was considered significant in the present study.

3. Results

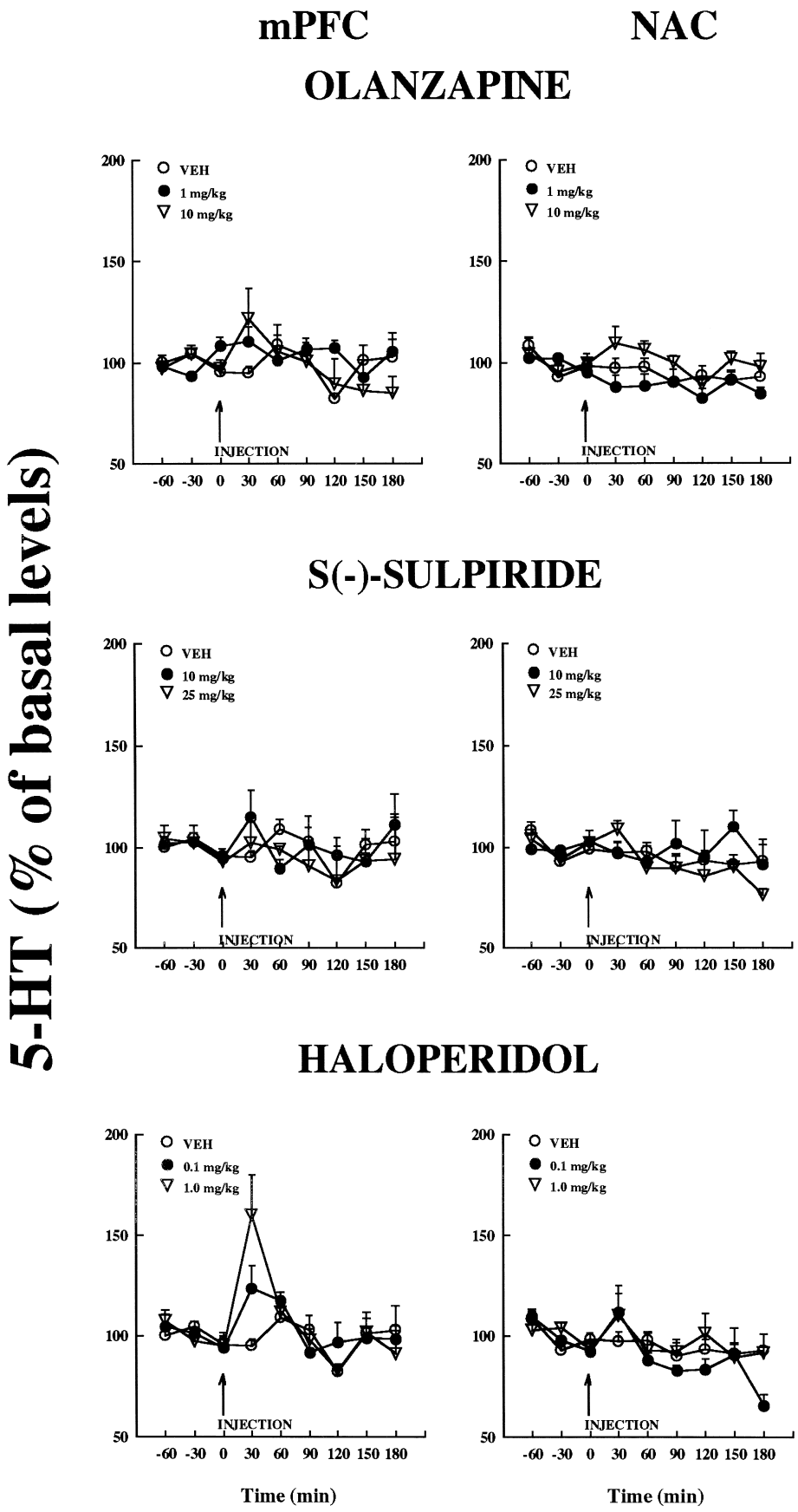
3.1. Basal extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens (Table 1)

There were no differences in basal extracellular 5-HT levels in the brain regions between the various treatment groups. Basal extracellular 5-HT levels were not different in the medial prefrontal cortex and the nucleus accumbens ($F(1,126) = 0.20$, $P = 0.66$). The vehicle injection did not affect basal extracellular 5-HT levels in either region.

3.2. The time-dependent effect of antipsychotic drugs and MDL-100,907 on extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens (Figs. 1–3)

In Fig. 1, repeated measures of ANOVA (treatment × time) demonstrated that amperozide (2 and 10 mg/kg) significantly increased extracellular 5-HT levels in the medial prefrontal cortex ($F(2,14) = 8.2$, $P = 0.004$) and the nucleus accumbens ($F(2,12) = 8.33$, $P = 0.005$). Clozapine (5 and 20 mg/kg) showed a significant main effect of the factor treatment in the nucleus accumbens ($F(2,16) = 4.15$, $P = 0.043$), but neither was significant within factors (time after injection) nor was there significant interaction between these factors. Post-hoc comparison indicated that clozapine (20 mg/kg) significantly increased extracellular 5-HT levels in the nucleus accumbens. Clozapine (5 and 20 mg/kg) had no effect on extracellular 5-HT levels in the medial prefrontal cortex. Risperidone (0.1 and 1 mg/kg) showed a significant main effect of the treatment ($F(2,13) = 5.23$, $P = 0.025$) and a significant main effect of time after injection ($F(5,13) =$

Fig. 2. Time-dependent effect of olanzapine (○: vehicle, ●: 1 and ▽: 10 mg/kg, s.c.) (top), *S*(−)-sulpiride (○: vehicle, ●: 10 and ▽: 25 mg/kg, s.c.) (middle) and haloperidol (○: vehicle, ●: 0.1 and ▽: 1.0 mg/kg, s.c.) (bottom) on extracellular 5-HT levels in the medial prefrontal cortex (mPFC, left) and the nucleus accumbens (NAC, right). The arrow indicates the drug injection time. Data are means ± S.E.M. ($N = 5–8$ for each treatment group) of corresponding time points, expressed as percentage of the pre-drug basal levels. Neither olanzapine (●: 1 and ▽: 10 mg/kg, s.c.), *S*(−)-sulpiride (●: 10 and ▽: 25 mg/kg, s.c.) nor haloperidol (●: 0.1 and ▽: 1.0 mg/kg, s.c.) had no significant effects on extracellular 5-HT levels in either region.


mPFC
NAC
OLANZAPINE
VEH
1 mg/kg
10 mg/kg
S(-)-SULPIRIDE
VEH
10 mg/kg
25 mg/kg
HALOPERIDOL
VEH
0.1 mg/kg
1.0 mg/kg
INJECTION
200
150
100
50
-60 -30 0 30 60 90 120 150 180
5-HT (% of basal levels)
Time (min)
Time (min)

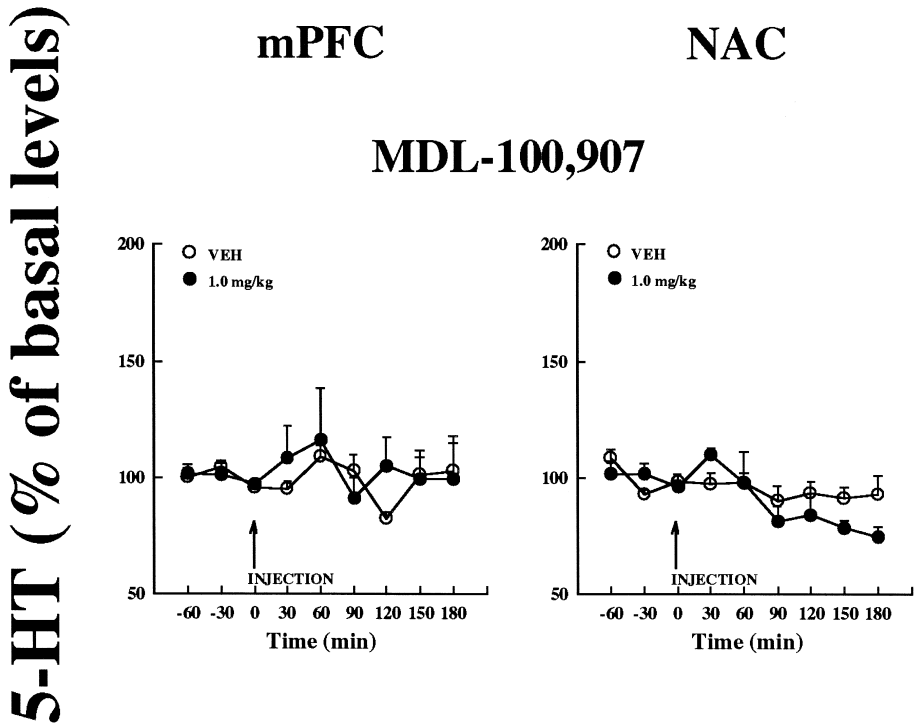


Fig. 3. Time-dependent effect of MDL-100,907 (○: vehicle and ●: 1 mg/kg, s.c.) on extracellular 5-HT levels in the medial prefrontal cortex (mPFC, left) and the nucleus accumbens (NAC, right). The arrow indicates the drug injection time. Data are means ± S.E.M. ($N = 4$–5 for each treatment group) of corresponding time points, expressed as percentages of the pre-drug basal levels. The MDL-100,907 (●: 1 mg/kg, s.c.) had no significant effect on extracellular 5-HT levels in either region.

2.42, $P = 0.047$) in the medial prefrontal cortex, but not a significant interaction between these factors. Post-hoc comparison indicated that risperidone (1 mg/kg) increased extracellular 5-HT levels in the medial prefrontal cortex. Risperidone (0.1 and 1 mg/kg) had no significant effect on extracellular 5-HT levels in the nucleus accumbens.

Olanzapine (1 and 10 mg/kg), haloperidol (0.1 and 1 mg/kg), *S*(−)-sulpiride (10 and 25 mg/kg) (Fig. 2) and MDL-100,907 (1 mg/kg) (Fig. 3) had no significant effect on extracellular 5-HT levels in either region. Haloperidol (1 mg/kg) produced a transient increase in extracellular 5-HT levels in the medial prefrontal cortex only in the first 30-min period after the injection ($F(1,11) = 8.24$, $P = 0.019$), as determined by one-way ANOVA.

4. Discussion

The present study demonstrated that some antipsychotic drugs modulate extracellular 5-HT levels in the medial prefrontal cortex and/or the nucleus accumbens in diverse ways. The medial prefrontal cortex is reported to have significant concentrations of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3 and 5-HT_7 receptors, while the nucleus accumbens has 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors (Leysen et al., 1996). Therefore, the increase in extracellular 5-HT levels in these two regions can be expected to have significant effects on mesolimbic and/or mesocortical 5-HT neurotransmission. If that is the case, the clinical effects of amperozide, clozapine and risperidone may be mediated by stimulation of 5-HT receptor subtypes other than 5-HT_{2A} receptors, in combination with 5-HT_{2A} receptor blockade. Antagonism of 5-HT_{2A} receptors per se does not appear to have significant effects on the ability to increase extracellular 5-HT levels in these two regions, since the selective 5-HT_{2A} receptor antagonist, MDL-100,907 (1 mg/kg) did not affect extracellular 5-HT levels.

Amperozide (2 and 10 mg/kg) increased extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens, consistent with recent findings (Hertel et al., 1997a). These effects may be due, in part, to inhibition of the reuptake of 5-HT (IC_{50} for the uptake for [^{3}H]5-HT = 0.32 μM; Pettersson, 1995). Clozapine suppresses the firing rate of 5-HT neurons of the dorsal raphe nucleus (Gallager and Aghajanian, 1976), possibly mediated by blockade of α_1-adrenoceptors, but not 5-HT_{2A} receptors (Lejeune et al., 1994). Clozapine has moderate affinity for 5-HT_{1A} receptors (Schotte et al., 1996) which inhibit 5-HT release (Hjorth and Sharp, 1991). Thus, clozapine would be expected to decrease 5-HT release from the 5-HT nerve terminals if clozapine is a 5-HT_{1A} receptor agonist. Ferré and Artigas (1995) have reported that both systemic administration (5 mg/kg, s.c.) and local perfusion (10 μM) of clozapine decreased 5-HT release while leaving dopamine release unaffected in the nucleus accumbens.

However, clozapine is also reported to antagonize the inhibition by 5-HT of K^+-stimulated [^{3}H]5-HT release from perfused synaptosomes of the nucleus accumbens (Drescher and Hetey, 1988), suggesting the facilitation of 5-HT release by clozapine via blockade of presynaptic 5-HT autoreceptors. In the present study, clozapine (20 mg/kg) significantly increased extracellular 5-HT levels in the nucleus accumbens while clozapine (5 mg/kg) had no effect in either region. The discrepancy between the results reported by Ferré and Artigas (1995) and the present findings are not readily explained. In our study, basal 5-HT levels in the dialysate (Table 1) were low as compared to those reported by Ferré and Artigas (1995). However, other authors also reported higher 5-HT levels in dialysate samples (Adell et al., 1991; Devaud et al., 1992; Petty et al., 1994; Hertel et al., 1996). In our study, the probe was perfused with artificial cerebrospinal fluid overnight for approximately 15 h after probe implantation. The basal extracellular 5-HT levels at that time were low as compared to those 2 or 3 h after acute implantation (data not shown). The extracellular 5-HT collected following overnight perfusion may be of neuronal origin to a greater extent than that collected after acute probe implantation. Ferré and Artigas (1995) reported a basal extracellular 5-HT level of 3.15 fmol/15 μl/30 min (0.21 ± 0.03 nM) per dialysate sample with a 2-mm long dialysis probe, which is much higher than the level reported in this study, 0.78 ± 0.04 fmol/10 μl/30 min, with the same length probe. The higher level of 5-HT in the study of Ferré and Artigas (1995) may represent some non-neuronal 5-HT from blood. A decrease in the amount of 5-HT in dialysate samples from blood could mask the effect of a drug on neuronal 5-HT. There are several other differences in the method such as the recovery period after surgery, three to five days in our study compared to 24 h (Ferré and Artigas, 1995). In addition, the difference in the strain and the age of the rats used, which is not mentioned in the study of Ferré and Artigas (1995), could also account for the discrepancy. Clearly, further studies are needed to reconcile the discrepant results.

Risperidone (1 mg/kg) increased extracellular 5-HT levels in the medial prefrontal cortex but not in the nucleus accumbens, in accordance with previous findings (Hertel et al., 1996). Interestingly, another 5-HT$_{2A}$/dopamine D$_2$ receptor antagonist, olanzapine (1 and 10 mg/kg) and the selective 5-HT$_{2A}$ receptor antagonist, MDL-100,907 (1 mg/kg) had no effect on extracellular 5-HT levels in either region (present data). These results clearly indicate that 5-HT$_{2A}$ receptor antagonism by itself does not contribute to the release of 5-HT in these two regions. The discrepancy between olanzapine and clozapine is noteworthy since these two drugs have a similar pharmacological profile, e.g., potent anti-α_1-adrenoceptors and anticholinergic effects, along with 5-HT$_{2A/2C}$ receptor antagonism and with relatively weak dopamine D$_2$ receptor antagonism (Schotte et al., 1996). They differ, however, in relative potency at 5-HT$_{1A}$, 5-HT$_7$ and 5-HT$_{1B/1D}$ receptors.

Table 1
Basal extracellular 5-HT levels in rat medial prefrontal cortex (mPFC) and nucleus accumbens (NAC)

Region (n)	5-HT
mPFC (67)	0.80 ± 0.03
NAC (61)	0.78 ± 0.04

Means $\pm$ S.E.M. (fmol/10 μl per 30 min).

The results reported here do not support the hypothesis of Hertel et al. (1997b) that the increase in extracellular 5-HT levels in the medial prefrontal cortex produced by risperidone is due to local α_2-adrenoceptor blockade on 5-HT nerve terminals since clozapine is also a potent α_2-adrenoceptor antagonist (Schotte et al., 1996) and did not increase extracellular 5-HT levels in the medial prefrontal cortex. Moreover, the suggestion of Hertel et al. (1997b) that risperidone-induced improvement in negative symptoms is due to increased 5-HT levels at some synapses in the central nervous system would also appear not to be supported by our data, since clozapine is effective in treating negative symptoms but did not increase extracellular 5-HT levels in the medial prefrontal cortex. Clozapine did increase extracellular 5-HT levels in the nucleus accumbens but neither risperidone or olanzapine increased extracellular 5-HT levels in the nucleus accumbens and both are effective in treating negative symptoms (Beasley et al., 1996). The results reported here suggest that the ability of olanzapine to improve negative symptoms is likely to be due to a non-serotonergic mechanism.

Haloperidol (0.1 and 1 mg/kg) did not increase extracellular 5-HT levels in either region. The present results are consistent with the results obtained with a higher dose of haloperidol (2 mg/kg) in the frontal cortex reported by Hertel et al. (1997a), but differ from those of Petty et al. (1994), who reported that doses of 5–20 mg/kg of haloperidol increased extracellular 5-HT levels in the medial prefrontal cortex. Interesting to note in our study, haloperidol (1 mg/kg) produced a transient increase in the extracellular 5-HT levels in the medial prefrontal cortex only in the first 30-min period after injection. This increase was significant ($P = 0.02$), as determined by one-way ANOVA, as compared with that of the vehicle-treated controls. The discrepancy between our results and the data from Petty et al. (1994) may be due to the difference in the doses used. Doses of 5–20 mg/kg may cause non-specific effects and may be less relevant to the effect at clinical doses. Similarly, the dopamine D$_{2/3}$ receptor antagonist, $S(-)$-sulpiride (10 and 25 mg/kg), had no effect on extracellular 5-HT levels in either region. Another dopamine D$_{2/3}$ receptor antagonist, raclopride and the dopamine D$_{2/3}$ receptor agonist, quinpirole have been reported to have no effect in the nucleus accumbens (Ferré and Artigas, 1995). These results suggest that the ability of

antipsychotic drugs to antagonize dopamine $D_{2/3}$ receptors may not affect extracellular 5-HT levels in the nucleus accumbens and perhaps medial prefrontal cortex.

An interaction between 5-HT and dopamine could partly account for the ability of amperozide, clozapine and risperidone to increase extracellular 5-HT levels. An increase in extracellular dopamine levels by local application of 5-HT through the dialysis probe has been demonstrated in both the nucleus accumbens (Parsons and Justice, 1993) and the medial prefrontal cortex (Iyer and Bradberry, 1996). Furthermore, the selective 5-HT reuptake inhibitor, fluoxetine, increases extracellular 5-HT levels in the medial prefrontal cortex (Tanda et al., 1996) and the nucleus accumbens (Ichikawa et al., unpublished data), whereas extracellular dopamine levels are increased in the medial prefrontal cortex (Tanda et al., 1996) and decreased in the nucleus accumbens by fluoxetine (Ichikawa and Meltzer, 1995). These results suggest that extracellular dopamine alone does not simply affect extracellular 5-HT levels.

The significance of the increase in extracellular 5-HT levels in these two regions induced by some antipsychotic drugs requires further study with additional drugs and chronic administration. The available data, which indicate significant differences among drugs of comparable efficacy, suggest that the ability to acutely increase extracellular 5-HT levels in the medial prefrontal cortex and nucleus accumbens may not be related to antipsychotic activity. However, these drugs do differ with regard to effects on negative and depressive symptoms and cognition. Alterations in serotonergic transmission have been reported to be correlated with negative symptoms of schizophrenia (e.g., emotional withdrawal, anergia and blunted affect) (Breier, 1995; Roth and Meltzer, 1995). Clozapine has been reported to be effective against treatment-resistant psychotic depression (Parsa et al., 1991; Dassa et al., 1993; Ranjan and Meltzer, 1996) and reduces both the number of affective episodes and rehospitalizations in patients with severe refractory bipolar illness (Banov et al., 1994; Zarate et al., 1995; Calabrese et al., 1996). The 5-HT function has also important effects on cognition (Buhot, 1997). The ability of antipsychotic drugs such as clozapine and risperidone to increase extracellular 5-HT levels in the nucleus accumbens and the medial prefrontal cortex, respectively, may be relevant to the differences between these drugs on these types of psychopathology.

5. Conclusions

Some antipsychotic drugs, such as amperozide, clozapine and risperidone, may modulate the release of 5-HT as well as dopamine. The failure of MDL-100,907 to affect extracellular 5-HT levels supports the conclusion that the increase in extracellular 5-HT levels elicited by some antipsychotic drugs is not directly related to their affinity for 5-HT_{2A} receptors.

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