Atypical Neuroleptics Enhance Histamine Turnover in Brain Via 5-Hydroxytryptamine$_{2A}$ Receptor Blockade$^1$


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ABSTRACT

Clozapine and olanzapine behave as weak H$_3$-receptor antagonists in vitro with $K_i$ values around 1 and 50 $\mu$M, respectively. Despite these modest apparent affinities, both compounds given orally to mice, nearly doubled steady-state tele-methylhistamine levels in brain, with ED$_{50}$ values as low as 1 and 3 mg/kg, respectively, an effect comparable to those of potent H$_3$-receptor antagonists. This effect corresponded to an enhancement of histamine turnover rate from 45 to 73 ng/g/h as measured in the case of olanzapine using the pargyline test. Other antipsychotics displaying, such as clozapine and olanzapine, high 5-hydroxytryptamine (5-HT)$_{2A}$ receptor antagonist potency, i.e., risperidone, thioridazine, seroquel, and iloperidone, also enhanced markedly tele-methylhistamine levels.

This effect was 1) additive with that of a pure H$_3$-receptor antagonist, ciproxifan, 2) mimicked by a 5-HT$_{2A}$ receptor antagonist, ketanserin, 3) reversed by a 5-HT$_{2A}$ receptor agonist, DOI, 4) not shared by antipsychotics with low affinity for the 5-HT$_{2A}$ receptor, i.e., haloperidol, sulpiride, raclopride, or remoxipride that, on the contrary, tended to reduce tele-methylhistamine levels. We conclude that in contrast to “typical” antipsychotics, “atypical” antipsychotics stimulate histamine neuron activity via blockade of the 5-HT$_{2A}$ receptor in vivo. This effect does not appear to account for their reduced extrapyramidal side-effects but may underlie their pro-cognitive properties.

During the last decade a number of novel antipsychotic drugs were developed with the aim of obtaining agents displaying therapeutic advantages over the first drug generation, often designated “typical” antipsychotic drugs. These include a lower propensity to elicit extrapyramidal side-effects, an improved therapeutic efficacy on negative and affective symptomatology of schizophrenia as well as on refractory forms of the disease. These drugs, often designated “atypical” antipsychotics, a rather vague terminology, were mostly modeled after clozapine, which seems to display such advantages but is not devoid of toxic side-effects (for reviews see Meltzer and Nash, 1991; Buchanan, 1995; Kinon and Lieberman, 1996). In addition to dopamine receptors blocked by all antipsychotics, clozapine potently blocks with $K_i$ of 1 to 20 nM a variety of amnergic receptors including muscarinic, $\alpha_1$ adrenergic, H$_3$ histaminergic, and 5-hydroxytryptamine (5-HT)$_{2A}$, 5-HT$_{2C}$, and 5-HT$_{7}$ serotonergic receptors. Although there are many individual differences among drugs designated “atypical antipsychotics”, all these compounds share some properties of clozapine, e.g., they display significant affinity toward several amnergic receptors and/or lower propensity to cause catalepsy in rodents as well as positive effects on animal models of cognition (reviewed by Arnt and Skarsfelt, 1998). To date the results of clinical studies have confirmed the predictions of lower incidence of extrapyramidal side-effects after administration of these novel antipsychotic drugs at doses that demonstrate antipsychotic efficacy. Controlled studies with some of these drugs, e.g., clozapine, risperidone, or olanzapine, have shown them to decrease negative symptomatology, whereas haloperidol is ineffective. It is not entirely clear to which receptor subtype(s) blockade, clozapine and these novel antipsychotic agents owe their peculiar animal behavioral and human clinical properties. Recently clozapine was shown to block the histamine H$_3$ receptor as evidenced on the release of noradrenaline or serotonin from brain slices and confirmed in radioligand binding assays, whereas typical antipsychotics were ineffective in this respect (Kathmann et al., 1994; Alves-Rodrigues et al., 1995).

In fact, the H$_3$ receptor was initially described as an inhibitory autoreceptor through which histamine controls its own synthesis in and release from tuberomammillary neurons in brain (Arrang et al., 1987), so that it could be predicted that its blockade by a drug like clozapine should enhance the activity of these neurons in vivo.

The role, if any, of histaminergic neurons in psychiatric

ABBREVIATIONS: HA, histamine; t-MeHA, tele-methylhistamine; (R)$\alpha$-MeHA, (R)$\alpha$-methylhistamine; HALO, haloperidol; CLZ, clozapine; OLZ, olanzapine; KET, ketanserin; CPX, ciproxifan; 5-HT, 5-hydroxytryptamine.
diseases is not well understood (Schwartz et al., 1995) but a relationship between histamine and schizophrenia is suggested by several pieces of evidence. In agreement, decreased H3 receptor-mediated response to histamine is consistently observed among schizophrenic patients (Rauscher et al., 1980; Nakai et al., 1991). Levels of tele-methylhistamine (t-MeHA), the major histamine metabolite in brain (Schwartz et al., 1971, 1991) are significantly enhanced in the cerebrospinal fluid of schizophrenic patients (Prell et al., 1995). Finally, a polymorphism within the H3 receptor gene was recently reported to be associated with schizophrenia (Orange et al., 1996).

We have evaluated the changes in histamine neuron activity induced in mice by administration of a variety of antipsychotic drugs by measuring the levels of t-MeHA in several brain regions.

Materials and Methods

[125I]iodoproxyfan Binding Assay. The procedure was that described by Ligneau et al. (1994). Aliquots of membrane suspension from mouse cerebral cortex, striatum, or hypothalamus (20 μg of protein) were incubated for 60 min at 25°C in 50 mM Na2HPO4/KH2PO4 buffer, pH 6.8 with [125I]iodoproxyfan alone or together with competing drugs. Specific binding was defined as that inhibited by 1 μM (R)-MeHA. Incubations were performed in triplicate and stopped by dilution with ice-cold medium, followed by rapid filtration through glass microfiber filters (GF/B Whatman, Clifton, NJ) pre-soaked in 0.3% polyethyleneimine. Radioactivity trapped on the filters was measured with a LKB (Rockville, MD) gamma counter (82% efficiency).

[3H]MeHA Release from Synaptosomes. Release experiments with synaptosomes were performed according to Arrang et al. (1985) with slight modifications (Garbarg et al., 1992). A crude synaptosomal preparation from mouse cerebral cortex was preincubated for 30 min with [3H]histidine (0.4 μM) at 37°C. Synaptosomes were then washed and resuspended in fresh 2 mM K+-Krebs-Ringer’s medium. After a 5-min preincubation in the presence of drugs, synaptosomes were incubated for 2 min with 2 or 30 mM K+. When required, (R)-MeHA (1 μM), a specific H3 receptor agonist (Arrang et al., 1987) was added to the medium. Incubations were ended by a rapid centrifugation and [3H]MeHA levels in the supernatant were determined (Garbarg et al., 1983).

t-MeHA Levels in Brain. Male Swiss mice (18–20 g) (Iffa-Credo, L’Arbresle, France) were fasted for 12 h before drug administration. Administrations were performed with drugs dissolved in 1% lactic acid and diluted as required in 1% methylocellulose or 0.9% NaCl for p.o. and i.p. administration, respectively. Rectal temperature of the animals was measured and, when necessary, maintained at 37°C by using a heating lamp. Animals were sacrificed by decapitation. The brain was dissected out and the cerebral cortex, striatum, and hypothalamus were homogenized in 10 volumes (w/v) of ice-cold perchloric acid (0.4 M). The perchloric acid extracts were centrifuged (4000 g for 20 min) and the supernatant was stored at −20°C. t-MeHA levels were determined by radioimmunoassay after derivatization of samples with benzoquinone as described previously (Garbarg et al., 1989b, 1992).

Assessment of Catalepsy. For assessment of catalepsy in an all-or-none manner, mice received haloperidol (0.25 mg/kg, i.p.) and, 1 h later, each mouse was placed gently so that both front limbs rested on top of a horizontal rod placed at a height of 5 cm above the floor. When required, H3-receptor ligands were given 1 h before haloperidol. An animal was considered to be in catalepsy if it remained with its hind legs on the floor and its front limbs on the rod for more than 5 s.

For assessment of catalepsy duration, mice received haloperidol (0.8 mg/kg, i.p.) and, 1 h later, were placed in the position described before. When required, H3-receptor ligands were administered 1 h before haloperidol. Scoring consisted in measuring the time during which they kept the position. Scoring were made under unblinded conditions.

Analysis of Data. Maximal effects, ED50, IC50 and pseudo Hill coefficients (nH) were determined by nonlinear regression using an iterative computer least-squares method and a one-site cooperative model (Parker and Waud, 1971). Kd values of drugs at the H3 receptor were calculated from their IC50 values, assuming a competitive antagonism and using the relationship Kd = IC50/(1 + S/Kd) where S and Kd represent, respectively, the concentration and the apparent dissociation constant of [125I]iodoproxyfan in binding experiments or the concentration and EC50 of histamine in release experiments (Cheng and Prusoff, 1973). Protein contents were determined according to the method of Lowry et al. (1951), using bovine serum albumin as the standard. Statistical evaluation of the results was by Student’s t test.

Radiochemicals and Drugs. The drugs and their sources were as follows: ciproxifan (cyclopropyl-4-(3-1H-imidazol-4-yl)propyloxyphe-nyl)(ketone), nafadotride and (Rα)-MeHA (Laboratoire Bioproiet, Paris, France), risperidone and iloperidone (Hoechst-Roussel Pharmaceuticals, Somerville, NJ), clozapine and thioridazine (Sandoz, Basel, Switzerland), olanzapine (Eli Lilly and Co., Indianapolis, IN), seroquel (Zeneca, Wilmington, DE), haloperidol (Janssen Pharmaceutica, Beerse, Belgium), raclopride and remoxipride (Astra, Lakemedel AB, Sweden), ketanserin and (−)-DOI (−)-2,5-dimethoxy-4-iodophenetamine hydrochloride (Research Biochemicals International, Natick, MA), (−)-sulpiride (Synthelabo, Paris, France), [125I]iodoproxyfan (2000 Ci/mmol) and t-(2S,5R)-H3 histidine (50 Ci/mmol) were purchased from Amersham (Amersham, UK). All drug weights are expressed as free base.

Results

Interaction of Clozapine and Olanzapine with the Histamine H3 Receptor. The specific binding of [125I]iodoproxyfan, a selective H3 receptor radioligand (Ligneau et al., 1994), to membranes from mouse cerebral cortex, striatum, and hypothalamus was monophasically inhibited by clozapine and olanzapine in increasing concentrations with pseudo Hill coefficients (nH) of 0.9 ± 0.1 and 0.9 ± 0.2, respectively (Fig. 1 and data not shown). Analysis of the displacement curve of the binding obtained in the three brain regions studied yielded IC50

Fig. 1. Inhibition by clozapine and olanzapine of [125I]iodoproxyfan binding to membranes from mouse striatum. Membranes were incubated for 1 h at 25°C with [125I]iodoproxyfan (30 μM) and drugs in increasing concentrations. Specific binding was defined as that displaced by 1 μM (Rα)-MeHA, corresponded to 71% of total and represented 72 ± 3 fmol/mg protein. Results are expressed as percentage of this value. Each point represents the mean of results from two to three different experiments with triplicate determinations.

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values of 2 to 5 μM for clozapine and 30 to 100 μM for olanzapine (Fig. 1 and data not shown). Taking into account a \( K_i \) value of 72 ± 9 pM for \([^{125}\text{I}]\)iodoproyfan, as determined from saturation kinetics at equilibrium in the three regions (data not shown), a calculated \( K_i \) value of 1 to 3 μM was found for clozapine and of 20 to 70 μM for olanzapine (Table 1).

Clozapine was examined for its ability to modulate HA release from cortical synaptosomes labeled with \( [^{3}\text{H}] \)histidine (Arrang et al., 1985). It failed to mimic the autoinhibitory effect of 1 μM exogenous HA but progressively and completely reversed it at the presynaptic \( H_3 \) receptor with an \( IC_{50} \) value of 10 ± 3 μM (Fig. 2). Taking into account an \( EC_{50} \) value of 0.06 μM for exogenous HA (Garbarg et al., 1992), an apparent \( K_i \) value of 0.6 μM was calculated for clozapine acting as an \( H_3 \)-receptor antagonist in this functional model.

**Effects of Typical and Atypical Antipsychotic Drugs on t-MeHA Levels.** The effects of 10 antipsychotic drugs belonging to various chemical classes and classified as either typical or atypical agents were analyzed on t-MeHA level, an index of HA neuronal activity in three mouse brain regions. In cerebral cortex, striatum, and hypothalamus, acute administration of haloperidol, sulphiride, raclopride, or remoxipride tended to slightly decrease (by ~10–30%) basal t-MeHA levels, but this inhibitory effect was hardly significant except in striatum (Fig. 3). In contrast, all other agents, sometimes classified as atypical antipsychotics, strongly and significantly enhanced t-MeHA level in the cerebral cortex, striatum, and hypothalamus. In the first two regions, the increase was of similar amplitude (about +80%) with all these compounds and in the same range as that observed after oral administration of the potent and selective HA \( H_2 \)-receptor antagonist ciproxifan (about +100%) (Ligneau et al., 1998), whereas it was of a lower amplitude (about +40%) in the hypothalamus (Fig. 3; Table 2). Clozapine, as well as olanzapine, displayed a similar potency at increasing t-MeHA levels in the three brain regions, with \( ED_{50} \) values of ~1 and ~3 mg/kg, respectively (Fig. 4 and Table 2). In the striatum, t-MeHA accumulation induced by oral administration of olanzapine was clearly additive with that induced by pargyline, a monoamine oxidase inhibitor and previously shown to be an index of neuronal HA turnover (Schwartz et al., 1991). In mice receiving pargyline, t-MeHA level increased linearly with time at a rate of 45 ng/g/h, which was enhanced to 73 ng/g/h in mice receiving pargyline and olanzapine (Fig. 5).

**Effects of Clozapine, Olanzapine, 5-HT2A Receptor Ligands, and Haloperidol on t-MeHA Levels in the Absence or Presence of a \( H_3 \)-Receptor Antagonist.** Oral administration of ciproxifan alone in a maximally effective dosage (3 mg/kg) (Ligneau et al., 1998) induced a doubling of t-MeHA levels in the cerebral cortex, striatum, and hypothalamus (Figs. 3 and 6). This effect of the \( H_3 \)-receptor antagonist was further enhanced by coadministration of clozapine, olanzapine, or ketanserin, a preferential 5-HT2A-receptor antagonist (Fig. 6). A significant increase in t-MeHA level was also observed 3 h after the administration of ketanserin alone (8 mg/kg, p.o.), as compared with control mice, in the cerebral cortex and striatum (+54 and +81%, respectively, Fig. 6) as well as hypothalamus (+42%, data not shown). The coadministration of ketanserin did not further enhance the effect of clozapine in the cerebral cortex and striatum (Fig. 7). DOI, a preferential 5-HT2A/2C-receptor agonist, did not change significantly t-MeHA level when used alone but strongly decreased the t-MeHA accumulation induced by clozapine (~62 and ~72% in the cerebral cortex and striatum, respectively) (Fig. 7). Given at a dose of 5 mg/kg DOI reversed the effect of clozapine by 58% (not shown). Prazosin (5 mg/kg, p.o.) an \( \alpha_1 \)-receptor antagonist did not modify t-MeHA levels.

Although it induced a slight and nonsignificant decrease in t-MeHA level (Figs. 3 and 8), haloperidol, a \( D_2 \)-like receptor antagonist, significantly inhibited by ~50% the t-MeHA accumulation induced by ciproxifan in the cerebral cortex, striatum (Fig. 8), and hypothalamus (not shown). This decreasing effect of haloperidol was not observed on the t-MeHA accumulation induced by coadministration of ketanserin (Fig. 8).

**Effect of (R)\(\alpha\)-MeHA and Ciproxifan on Catalepsy in Mice.** (R)\(\alpha\)-MeHA or ciproxifan, tested in a maximally effective dosage (20 and 3 mg/kg, respectively) (Garbarg et al., 1989a; Ligneau et al., 1998), neither produced any significant catalepsy when administered alone nor modified haloperidol-induced catalepsy in mice (Table 3).

## Discussion

Our main finding is that clozapine, as well as a number of other atypical antipsychotic drugs, activate cerebral histaminergic neurons, as judged from the enhanced level of t-MeHA they induce in several brain areas.

This was not unexpected in the case of clozapine, a drug previously shown to be unique among antipsychotics in that it displays significant antagonist activity at the \( H_3 \)-heterore-
ceptor controlling \(^{3}\text{H}\)noradrenaline release in brain slices as well as in radioligand binding tests (Kathmann et al., 1994; Alves-Rodrigues et al., 1995). In this study, we have confirmed this activity, showing that the drug reverses the action of histamine at the \(H_{3}\)-autoreceptor, controlling \(^{3}\text{H}\)HA release from synaptosomes (Arrang et al., 1985; Garbarg et al., 1992) and inhibits \(^{125}\text{I}\)iodoproxyfan binding to cerebral membranes (Ligneau et al., 1994). The apparent \(K_{i}\) value (about 1 \(\mu\text{M}\)) of clozapine at \(H_{3}\) receptors regulating HA release is in the same range as that reported at \(H_{3}\) receptors regulating noradrenaline (Kathmann et al., 1994) or serotonin (Alves-Rodrigues et al., 1995) release. These similar \(K_{i}\) values at \(H_{3}\) receptors of a nonimidazole compound further argue against the existence of several \(H_{3}\) receptor subtypes previously suggested by functional studies (Clapham and Kilpatrick, 1992; Leurs et al., 1996; Schlicker et al., 1996). The clozapine-related atypical antipsychotic drug olanzapine also inhibited \(^{125}\text{I}\)iodoproxyfan binding at the \(H_{3}\) receptor but with a very modest potency, its apparent \(K_{i}\) value being of about 50 \(\mu\text{M}\).

Many previous studies, using thioperamide and a variety of other antagonists, have shown that \(H_{3}\)-receptor blockade in vivo activates histaminergic neuron activity (Schwartz et al., 1991, 1995) and enhances \(^{3}\text{H}\)histamine synthesis (Arrang et al., 1987), endogenous HA release (Itoh et al., 1991; Mochizuki et al., 1991), and levels of \(t\)-MeHA, a major metabolite in brain (Garbarg et al., 1989a,b; Oishi et al., 1989). These effects all reflect the tonic inhibition of histaminergic neurons that endogenous HA exerts via \(H_{3}\)-autoreceptors and no other tonic inhibitory mechanism controlling the activity of these neurons has been reported. In addition, clozapine administration resulted in an enhancement of \(t\)-MeHA levels of about 100%, i.e., in the same range as that elicited by \(H_{3}\)-receptor antagonists such as thioperamide (Garbarg et al., 1989a) or ciproxifan (Ligneau et al., 1998 and present data). Also, as in the case of \(H_{3}\)-receptor antagonists (Schwartz et al., 1991), the effect of clozapine on steady-state \(t\)-MeHA levels resulted from an enhanced HA turnover rate, shown to be nearly doubled according to its evaluation via measurement of pargyline-induced \(t\)-MeHA accumulation (see Results).

Nevertheless, despite these various observations, several findings led us to the conclusion that this effect could not be ascribed to blockade of \(H_{3}\) receptors. First, in vitro, clozapine

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**Table 2**

Effects of clozapine and olanzapine on \(t\)-MeHA levels in various mouse brain regions

<table>
<thead>
<tr>
<th></th>
<th>Hypothalamus</th>
<th>Striatum</th>
<th>Cerebral cortex</th>
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<tr>
<td>ED(_{50}) (mg/kg)</td>
<td>1.5 ± 0.6</td>
<td>0.9 ± 0.2</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>Maximal Effect (% of Control)</td>
<td>148 ± 4</td>
<td>182 ± 3</td>
<td>182 ± 6</td>
</tr>
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**Fig. 3.** Effects of typical and atypical antipsychotics on \(t\)-MeHA levels in three brain regions. Mice were sacrificed 3 h after the oral administration of vehicle, haloperidol (1 mg/kg), ciproxifan (3 mg/kg), raclopride, remoxipride, risperidone (5 mg/kg), iloperidone (20 mg/kg), thioridazine, seroquel, clozapine, olanzapine (30 mg/kg), or sulpiride (100 mg/kg). Results from at least 15 mice are expressed as percent change as compared with control \(t\)-MeHA levels (59 ± 2, 112 ± 4, and 272 ± 6 ng/g in the cerebral cortex, striatum and hypothalamus respectively). *\(^{P} < 0.05\), **\(^{P} < 0.01\), ***\(^{P} < 0.001\) as compared with controls.

**Fig. 4.** Changes in \(t\)-MeHA levels in mice receiving clozapine (○) or olanzapine (●) in increasing dosages. Mice were sacrificed 3 h after oral administration of the drug. Values are means ± S.E.M. from 12 to 20 animals.
was 100 to 1000 times less potent at the H₃-receptor than thioperamide, both in binding and release experiments. However, its in vivo effect surprisingly occurred with an ED₅₀ value in the same milligram per kilogram range (Fig. 4; Table 2) as that previously reported for thioperamide in the same test (Garbarg et al., 1989a). Even more strikingly, an effect of similar amplitude and occurring with a similarly low ED₅₀ value (3 mg/kg) was obtained for olanzapine which displays a 50-fold lower potency than clozapine at the H₃ receptor in vitro and the same increase in t-MeHA levels could be observed with various other atypical antipsychotics that display low, if any, affinity at this receptor (Schlicker and Marr, 1996). Second, the effects of clozapine and olanza-

**Fig. 5.** Time course of the changes in striatal t-MeHA levels in mice treated with pargyline and/or olanzapine. Mice were sacrificed at various times after the administration of olanzapine (30 mg/kg, p.o.) and/or pargyline (85 mg/kg, i.p.). Values are means ± S.E.M. from 12 to 18 animals. *P < .01, **P < .001 as compared with controls; §P < .01 as compared with pargyline alone.

**Fig. 6.** The increase in t-MeHA level induced by clozapine (CLZ, 30 mg/kg), olanzapine (OLZ, 30 mg/kg), or ketanserin (KET, 8 mg/kg) is additive with that induced by ciproxifan (CPX, 3 mg/kg), a H₃-receptor antagonist. Mice were sacrificed 3 h after oral administration of vehicle or drug. Values are means ± S.E.M. from 12 to 18 animals. *P < .01, **P < .001 as compared with controls; §P < .05, §§P < .01 as compared with ciproxifan alone.

**Fig. 7.** Effect of ketanserin and DOI, a preferential 5-HT₂A-receptor antagonist and agonist, respectively on the t-MeHA accumulation induced by cloza-
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neuroleptics (Meltzer and Nash, 1991). Accordingly, these compounds elicit a predominant 5-HT2A receptor occupancy in vivo accompanied by a moderate D2-receptor occupancy, a balance proposed to underlie their atypical profile (Brunello et al., 1995; Schotte et al., 1996; Busatto and Kerwin, 1997). It was therefore of interest to assess the effect of 5-HT2A-receptor ligands on HA neuron activity. Ketanserin, a preferential 5-HT2A receptor antagonist, mimicked the enhancing effect of atypical antipsychotics on t-MeHA levels in mouse cerebral cortex, striatum, and hypothalamus and, like that of the latters, its effect was additive with that induced by ciproxifan (Fig. 6). DOI, a 5-HT2A2C-receptor agonist, did not modify t-MeHA level but strongly reversed the effect of clozapine. Our findings therefore show that endogenous serotonin tonically inhibits HA neurons via 5-HT2A receptors, an effect blocked by clozapine. These 5-HT2A receptors could be located on HA neurons themselves, on interneurons or nearby axon terminals impinging on the formers. This inhibitory effect of serotonin was apparently never described before but the 5-HT2A receptor displays inhibitory effects on the neurotransmission as neither ciproxifan nor a H3-receptor agonist did modify t-MeHA levels but, on the contrary, tended to decrease it. This inhibitory effect was particularly clear in striatum (Fig. 3) or, in other regions, when t-MeHA levels had been enhanced by treatment with ciproxifan (Fig. 8 and data not shown). It is consistent with the findings that endogenous dopamine released by administration of amphetamine enhances striatal HA release by interacting with D2-like receptors (Ito et al., 1996). It is interesting to underline that the tendency of antipsychotic drugs to inhibit HA neuron activity via blockade of D2-like receptors is dramatically reversed by ketanserin or with atypical compounds displaying significant affinity for the 5-HT2A receptor.

Two main therapeutical advantages of atypical over typical antipsychotics seem to derive from blockade of the 5-HT2A receptor they induce, in addition to that of D2-like (D2 and D3) receptors, that may potentially be related to enhanced HA neuron activity. The first one is a reduced propensity to elicit motor side-effects, exemplified by a reduced cataleptogenic activity in rodents (Meltzer and Nash, 1991; Arnt and Skarsfeldt, 1998). Although a role for the H3 receptor present on striatonigral neurons can be evoked (Garcia et al., 1997), this property of clozapine and atypical antipsychotic drugs cannot be ascribed to enhanced HA neuron activity inasmuch as neither ciproxifan nor a H3-receptor antagonist did modify haloperidol-induced catalepsy (Table 3).

The second advantage of atypical antipsychotics is their arousing and pro-cognitive effects resulting in a significant efficacy against negative symptomatology (Kinon and Lieberman, 1996). The positive functional role attributed to HA neurons in processes such as wakefulness, attention, and cognition (Schwartz et al., 1991, 1995) allows to propose that this property of atypical antipsychotics could be related to their unique ability to activate HA neurons. In agreement, activation of these neurons by H3-receptor blockade is accompanied in cats and/or rodents with increase of vigilance, and fast cortical rhythms as well as improved attention and learning ability (Lin et al. 1990; Meguro et al., 1995; Miyazaki et al., 1995). Hence

**TABLE 3**

Effects of a histamine H3-receptor agonist or antagonist on haloperidol-induced catalepsy

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Catalpse</th>
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<tr>
<td>All-or-none scoring (no. of cataleptic mice)</td>
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</tr>
<tr>
<td>Haloperidol (0.25)</td>
<td>6/10</td>
</tr>
<tr>
<td>(R)α-MeHA (20)</td>
<td>0/10</td>
</tr>
<tr>
<td>Haloperidol + (R)α-MeHA</td>
<td>5/10</td>
</tr>
<tr>
<td>Haloperidol (0.25)</td>
<td>14/22</td>
</tr>
<tr>
<td>Ciproxifan (3)</td>
<td>2/18</td>
</tr>
<tr>
<td>Haloperidol + ciproxifan</td>
<td>15/22</td>
</tr>
<tr>
<td>Duration of catalepsy (in sec, n = 20–40)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol (0.8)</td>
<td>121 ± 10</td>
</tr>
<tr>
<td>Haloperidol (0.8) + (R)α-MeHA (20)</td>
<td>143 ± 14</td>
</tr>
<tr>
<td>Haloperidol (0.8) + ciproxifan (3)</td>
<td>128 ± 16</td>
</tr>
</tbody>
</table>

Drugs were administered intraperitoneally at the indicated dosage (mg/kg). H3-receptor ligands were administered 2 h and haloperidol 1 h before assessment of catalepsy.
our observation that the positive effect of atypical antipsychotic drugs on HA neuron activity can be further enhanced by a H3-receptor antagonist, suggests the potential usefulness of this class of drugs in schizophrenia.

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References
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