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ORIGINAL ARTICLE

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JL13, a pyridobenzoxazepine compound with potential atypical antipsychotic activity, increases extracellular dopamine in the prefrontal cortex, but not in the striatum and the nucleus accumbens of rats

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Abstract In behavioral and receptor binding studies, 5-(4-methylpiperazin-1-yl)-8-chloro-pyridol{2,3b}{1,5}benzoxazepine (JL13) shows an atypical antipsychotic profile. We used microdialysis in awake rats to study the effects of various intraperitoneal doses of JL13 on extracellular concentrations of dopamine in the prefrontal cortex, nucleus accumbens and striatum. JL13 at 20 mg/kg and 40 mg/kg dose-dependently raised extracellular dopamine (234% and 434% of basal levels at peak, respectively) in the prefrontal cortex whereas lower doses (5 mg/kg and 10 mg/kg) had no effect. Extracellular concentrations of dihydroxyphenylacetic acid and homovanillic acid were also significantly increased in the prefrontal cortex of rats given 40 mg/kg JL13 (310% and 230% of basal levels, respectively). At 20 mg/kg and 40 mg/kg JL13 did not affect the extracellular concentrations of dopamine and its metabolites in the striatum and nucleus accumbens.

The mechanisms by which JL13 increases cortical dopamine release and the significance for potential antipsychotic efficacy are discussed.

Key words Antipsychotic drugs · Dopamine receptors · Dopamine release · JL13 · Microdialysis · Nucleus accumbens · Prefrontal cortex · Striatum

Introduction

Clozapine is the prototype atypical antipsychotic compound with greater therapeutic efficacy and fewer extrapyramidal side-effects (Kane et al. 1988). Interactions with different types of receptors are considered to contribute to its characterization as atypical (Kinon and Lieberman 1996). It has been suggested that a greater relative affinity for serotonin 5-HT_2 than for dopamine (DA) D_2 receptors contributes to the attenuated extrapyramidal side-effects and improvement of certain negative symptoms (Meltzer et al. 1989). The finding that clozapine has a much greater affinity for the D_4 than for the D_2 receptor (Van Tol et al. 1991), and that the D_4 receptors are localized at high density in the frontal cortex and practically absent in the dorsal striatum (Ariano et al. 1997; Primus et al. 1997; Tarazi et al. 1997), have led to the suggestion that D_4 receptors may be an important target for the atypical properties of clozapine.

The clinical expression of schizophrenia involves deficits in cognitive abilities such as working memory and attention, in addition to positive and negative symptoms (Saykin et al. 1991). Although selective D_4 receptor blockers have no antipsychotic efficacy (Kramer et al. 1997), in monkeys blockade of these receptors reversed the cognitive deficit caused by the psychomimetic drug phencyclidine (Jentsch et al. 1999). These findings suggest that blockade of D_4 receptors may alleviate some cognitive deficits in schizophrenic patients.

An interesting characteristic of clozapine and other atypical antipsychotic compounds is that they selectively increase extracellular DA in the prefrontal cortex whereas typical antipsychotics such as haloperidol raise extracellular DA more in the striatum than in the prefrontal cortex (Moghaddam and Bunney 1990). The mechanism of clozapine's selective effect on cortical DA is not known, but blockade of D_4 or 5-HT_{2A} receptors or stimulation of 5-HT_{1A} receptors may contribute (Schmidt and Fadayel 1995; Rollema et al. 1997; Broderick and Piercey 1998). In view of the suggestion that a reduced DA activity in mesocortical projections is involved in negative symptoms (Weinberger and Lipska 1995), clozapine's efficacy on these symptoms may be related to its ability to increase extracellular DA in the prefrontal cortex. Unfortunately, clozapine can cause a potential fatal agranulocytosis and this has limited its use to patients refractory to other medication (Krupp and Barnes 1989). This has prompted efforts to develop new antipsychotic drugs that reproduce its receptor profile.

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JL13 [5-(4-methylpiperazin-1-yl)-8-chloro-pyridol{2,3b}{1,5} benzoxazepine] has high affinities for 5-HT_{2A} and D_4 receptors (K_i=60 nM and 109 nM) and lower affinities for D_2 (K_i=1.2 μM), cholinergic muscarinic (K_i>1 μM) and 5-HT_{2C} (K_i>10 μM) receptors (Liégeois et al. 1994; Bruhwyler et al. 1997; Therabel, data on file). Consistently with the atypical antipsychotic profile displayed in binding studies, JL13 antagonized apomorphine-induced climbing in mice but did not modify apomorphine-induced stereotypy or cause catalepsy (Bruhwyler et al. 1997), suggesting that, similarly to clozapine, JL13 preferentially antagonizes the responses mediated by the enhancement of dopaminergic transmission in the mesolimbic system (Ljungberg and Ungerstedt 1978).

The aim of the present study was to examine whether JL13 selectively affects dopaminergic transmission in the prefrontal cortex, as predicted by its atypical antipsychotic profile. Using microdialysis in awake rats, we studied the effects of various intraperitoneal doses (5–40 mg/kg) of JL13 on extracellular concentrations of DA in the striatum, nucleus accumbens and prefrontal cortex.

Materials and methods

Animals. Male rats (CD-COBS; Charles River, Italy) weighing 250–300 g were housed at constant temperature (21±1°C) and relative humidity (60±5%) under a regular light-dark schedule (lights on at 7:00–19:00 h) with food and water freely available.

Procedures involving animals and their care are conducted in conformity with the institutional guidelines that are in compliance with national (D.L. no. 116, G.U., Suppl. 40, 18 February 1992, Circolare no. 8, G.U., 14 July 1994) and international (EEC Council Directive 86/609, OJ L 358,1, December 12, 1987; Guide for the Care and Use of Laboratory Animals, U.S. National Research Council, 1996) laws and policies.

Dialysis procedure. Dialysis experiments were conducted in awake, freely moving rats; each rat was implanted with a single probe. Rats were anesthetized with 3.5 ml/kg equithesin (prepared by mixing 1.2 g pentobarbital, 5.3 g chloral hydrate, 2.7 g $MgSO_4$, 49.5 ml propylene glycol, 12.5 ml ethanol and 58 ml distilled water) and placed on a stereotaxic apparatus (David Kopf Instruments, Tujunga, Calif., USA). A hole was drilled in the skull and a small incision made in the dura with a bent needle tip. The probes, perfused with artificial cerebrospinal fluid (aCSF), were lowered slowly into the rat nucleus accumbens, antero-lateral striatum or prefrontal cortex and fixed vertically to the skull using two anchorage screws and acrylic cement. Stereotaxic coordinates were as follows: nucleus accumbens: AP=+10.9, L=±1.6 and V=+1.8; striatum: AP=+9.7, L=±3.4 and V=+3.4; prefrontal cortex: AP=+4.3, L=±0.6 and V=–5.0 from the interaural line or bregma (prefrontal cortex) according to the Paxinos and Watson (1982) atlas. "I"-shaped dialysis probes were prepared essentially as described by Robinson and Wishaw (1988) except that the dialysis membranes were made of polyacrylonitrile-sodium methallyl sulphonate (AN 69 Hospal S.p.A.; 310 μm outer diameter, 240 μm inner diameter; 55 kDa cut-off). The length of exposed membrane was 4 mm for the prefrontal cortex and 2 mm for the striatum and nucleus accumbens.

Rats were allowed to recover from anesthesia one per cage with free access to food and water. About 24 h after surgery each rat was placed in a cage and the inlet cannula connected by polyethylene tubing to a 2.5 ml plastic syringe containing aCSF (composition in mM: 145 NaCl, 3 KCl, 1.26 $CaCl_2 \times 2H_2O$, 1 $MgCl_2 \times 6H_2O$ in distilled water and buffered at pH 7.4 with 2 mM sodium phosphate buffer). Each probe was perfused at a constant flow-rate of 2 μl/min with a CMA/100 microinfusion pump (CMA/Microdialysis, Stockolm, Sweden).

After a 30-min washout period, consecutive 20-min samples of perfusate containing DA, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were collected in minivials and directly assayed by high performance liquid chromatography with electrochemical detection as previously described (Invernizzi et al. 1990). DA was separated through a 150×4.6 mm column (Supelcosil LC18-DB, 3 μm; Supelco, Bellefonte, Pa., USA) using a mobile phase containing 0.1 M sodium acetate, 0.34 mM sodium octyl sulfate, 0.1 mM Na_2EDTA, 60 ml/l CH_3OH, pH 4.2 with acetic acid. A constant flow-rate of 1 ml/min was maintained by a Gilson pump (mod. 307; Gilson, France). DA, DOPAC and HVA were measured by a Coulochem II electrochemical detector equipped with a 5011 analytical cell. The first electrode was set at +300 mV and the second at –325 mV. DOPAC and HVA were read as first and DA as second electrode output signal.

Basal levels of DA, DOPAC and HVA in fmol/40 μl, respectively, were: prefrontal cortex, 20.2±1.5 (n=35), 491±36 (n=35), 125±10 (n=33); striatum, 70.4±8.2 (n=17), 18.4±1.1 (n=17), 6.8±0.5 (n=17); nucleus accumbens, 63.7±7.7 (n=18), 22.8±2.2 (n=17), 5.1±0.4 (n=17).

Histological procedure. At the end of the experiments rats were deeply anesthetized with 400 mg/kg chloral hydrate and killed by decapitation; their brains were immediately removed and frozen on dry-ice. Probe tracks were examined on 40-μm coronal sections from the prefrontal cortex, nucleus accumbens and striatum of each rat. Only rats with correct probe placement were considered in the results (35/41 for prefrontal cortex, 17/19 for nucleus accumbens and 17/18 for striatum).

Drug treatment. Once the basal extracellular concentrations of DA and its metabolites were stable (at least three consecutive samples differing less than 15% of the mean basal value), rats were injected intraperitoneally with vehicle or 5, 10, 20 and 40 mg/kg (as base) JL13 fumarate [5-(4-methylpiperazin-1-yl)-8-chloro-pyridol{2,3b}{1,5}benzoxazepine; Therabel Research; Brussels, Belgium]. The concentrations of DA, DOPAC and HVA were measured in dialysate samples over 180 min after injection.

JL13 fumarate was dissolved in 1 ml of 1 M HCl and the solution was buffered to pH 4.5/5.0 with 1 M NaOH. JL13 (5–20 mg/kg) was injected in 4 ml/kg. On account of the low solubility, the dose of 40 mg/kg was injected in 8 ml/kg. Vehicles received acidified NaCl solution.

Statistical analysis. The effects of the different doses of JL13 on regional extracellular DA, DOPAC and HVA were examined by ANOVA for repeated measures with treatment (tr) as between subjects and time (t) as within subject factors. Post-hoc comparisons were made by Tukey's test.

Values missing because of occasional problems in sample collection or analysis were replaced by the mean of the samples immediately before and after.

Results

Effect of JL13 on extracellular DA in the prefrontal cortex, nucleus accumbens and striatum

The vehicle tended to increase cortical extracellular DA by 34% from basal values 20 min and 40 min after injection, but the effect was not significant. Doses of 20 mg/kg and 40 mg/kg JL13 significantly raised extracellular DA [234% and 434% of basal values at peak; Fig. 1; $Ftr(4,30)=6.0$, $P<0.01$; $Ft(9,270)=31.6$, $P<0.01$; $Ftrxt(36,270)=7.0$, $P<0.01$]. Extracellular DA in rats

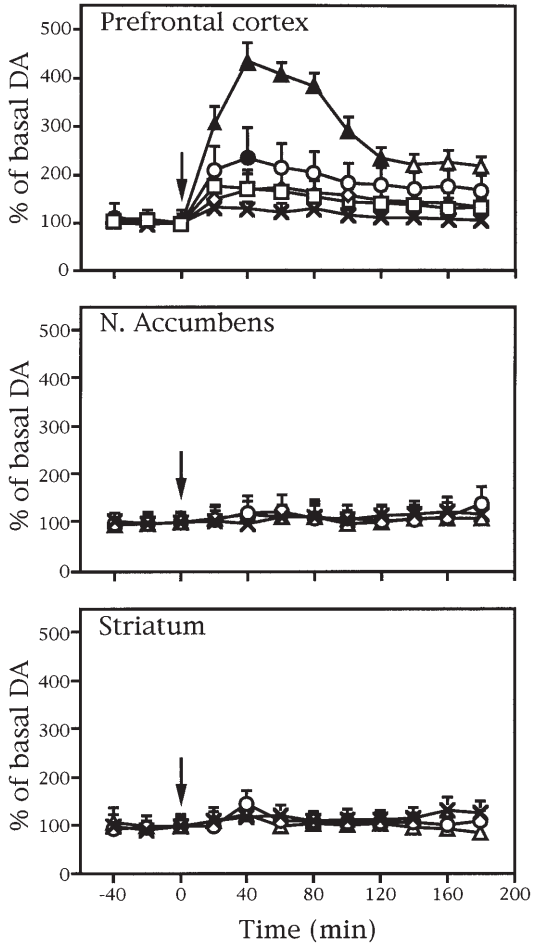

Fig. 1 Extracellular DA in the prefrontal cortex, nucleus accumbens and striatum of rats given vehicle (✕), 5 (❑), 10 (✧), 20 (○) and 40 (△) mg/kg JL13. Data are means ± SEM of 5–8 rats. *Arrows* indicate the injection of vehicle or JL13. *Solid symbols* indicate $P<0.05$ vs. vehicle (Tukey's test)

given 40 mg/kg JL13 was significantly higher ($P<0.05$) than after vehicle from 20 min to 120 min after injection, whereas in rats given 20 mg/kg JL13, a significant effect was observed at 40 min ($P<0.05$). Extracellular DA concentrations in rats given 5 mg/kg and 10 mg/kg JL13 were not different from vehicle-treated rats.

Vehicle, 20 mg/kg and 40 mg/kg JL13 had no effect on extracellular DA in striatum [$Ftr(2,14)=0.2$, $P>0.05$; $Ft(9,126)=2.1$, $P<0.05$; $Ftrxt(18,126)=1.0$, $P>0.05$] and nucleus accumbens [$Ftr(2,15)=0.7$, $P>0.05$; $Ft(9,135)=2.4$, $P<0.05$; $Ftrxt(18,135)=1.0$, $P>0.05$; Fig. 1].

Effect of JL13 on extracellular DOPAC and HVA in the prefrontal cortex, nucleus accumbens and striatum

Extracellular DOPAC in the prefrontal cortex increased, not significantly, 40 min and 60 min after vehicle (+36%) whereas a significant increase ($P<0.05$, Tukey's test) in extracellular HVA was found 60 min (+32%) and 120 min (+28%) after vehicle (Fig. 2).

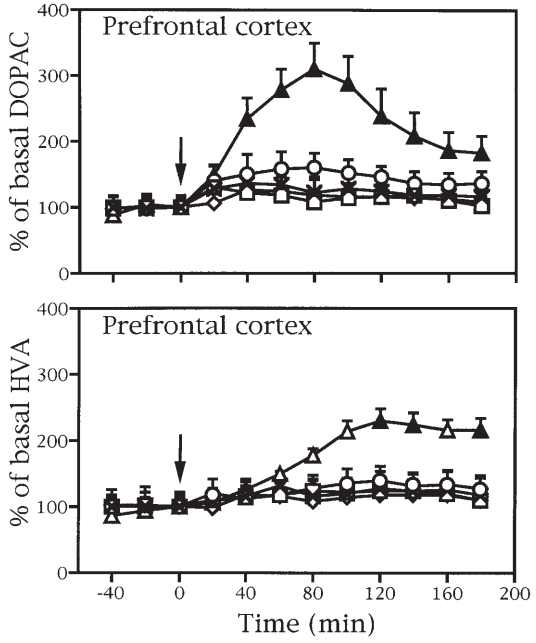

Fig. 2 Extracellular DOPAC and HVA in the prefrontal cortex of rats given vehicle (✕), 5 (❑), 10 (✧), 20 (○) and 40 (△) mg/kg JL13. Data are means ± SEM of 6–7 rats. *Arrows* indicate the injection of vehicle or JL13. *Solid symbols* indicate $P<0.05$ vs. vehicle (Tukey's test)

Extracellular DOPAC and HVA were significantly increased in the prefrontal cortex of rats given 40 mg/kg JL13 (Fig. 2). DOPAC [$Ftr(4,29)=12.9$, $P<0.01$; $Ft(9,261)=19.0$, $P<0.01$; $Ftrxt(36,261)=9.8$, $P<0.01$] was maximally increased at 80 min after injection (310% of basal values) whereas HVA [$Ftr(4,30)=1.6$, $P>0.05$; $Ft(9,270)=23.5$, $P<0.01$; $Ftrxt(36,270)=7.4$, $P<0.01$] peaked at 120 min (230% of basal values).

Extracellular concentrations of DOPAC and HVA were not modified by any dose of JL13 in striatum [DOPAC, $Ftr(2,14)=0.1$, $P>0.05$; $Ft(9,126)=2.3$, $P<0.05$; $Ftrxt(18,126)=1.0$, $P>0.05$; HVA, $Ftr(2,14)=1.6$, $P>0.05$; $Ft(9,126)=0.6$, $P>0.05$; $Ftrxt(18,126)=0.7$, $P>0.05$] and nucleus accumbens [DOPAC, $Ftr(2,14)=0.5$, $P>0.05$; $Ft(9,126)=2.7$, $P<0.01$; $Ftrxt(18,126)=1.4$, $P>0.05$; HVA, $Ftr(2,14)=1.3$, $P>0.05$; $Ft(9,126)=1.3$, $P>0.05$; $Ftrxt(18,126)=1.0$, $P>0.05$; data not shown].

Discussion

Doses of 20 mg/kg and 40 mg/kg JL13 significantly raised extracellular DA in the prefrontal cortex with no effect on dialysate DA in striatum and nucleus accumbens. The mechanism by which JL13 and other atypical antipsychotics (Moghaddam and Bunney 1990; Nomikos et al. 1994; Invernizzi et al. 1995; Kinon and Lieberman 1996) preferentially increase extracellular DA in the prefrontal cortex is not clear.

JL13, like clozapine (K_i=4 nM) and other atypical antipsychotics (Roth and Meltzer 1995; Blin 1999), has high

affinity for 5-HT_{2A} receptors (K_i=60 nM; Bruhwyler et al. 1997; Therabel, data on file). Selective antagonists at these receptors such as M100,907 preferentially increase extracellular DA in the prefrontal cortex (Schmidt and Fadayel 1995). High densities of 5-HT_{2A} receptor binding are found in the prefrontal cortex (Hamada et al. 1998) whereas the levels of these sites are lower in subcortical regions such as striatum and nucleus accumbens (Pazos et al. 1985). In view of the finding that administration of M100,907 injected into the prefrontal cortex significantly increased extracellular DA in this region (Schmidt and Fadayel 1995), a local action on 5-HT_{2A} receptors may be involved in JL13's ability to preferentially increase cortical extracellular DA. Blockade of 5-HT_{2C} receptors which also raises extracellular DA in the prefrontal cortex (Millan et al. 1998a) was not involved, since JL13 is not active on these receptors (Bruhwyler et al. 1997).

The fact that JL13 has low affinity for D_2 binding (Liégeois et al. 1994) and, unlike potent antagonists at these receptors, had no effect on extracellular DA in the striatum and nucleus accumbens makes it unlikely that D_2 receptor blockade was involved in its effect on cortical dialysate DA.

There has been much interest in the role of D_4 receptors in the mechanism of action of clozapine and other antipsychotics, and JL13, like clozapine (K_i=9 nM; Van Tol et al. 1991), has high affinity for these receptors (K_i=109 nM; Therabel, data on file). D_4 receptors are localized mainly in cortical and limbic structures and are almost absent in the dorsal striatum (Ariano et al. 1997; Primus et al. 1997; Tarazi et al. 1997). There are reports that selective D_4 receptor antagonists such as PNU-101387 (Broderick and Piercey 1998), S18126 and L745,870 (Millan et al. 1998b) preferentially increase extracellular DA in the prefrontal cortex, but it has recently been argued that this occurs at doses well above those believed to block D_4 receptors selectively (Millan et al. 1998b).

Although direct measurements of in vivo occupation of cortical D_4 receptors are needed to clarify this issue, we found recently that local administration of 0.01–1 μM L745,870 in the prefrontal cortex did not modify extracellular DA in this region (unpublished results). It seems therefore that blockade of D_4 receptors in the prefrontal cortex is not associated with increased DA release.

Whatever the mechanism involved, the functional significance of increased DA release in the prefrontal cortex of schizophrenic patients merits some consideration. Negative symptoms in schizophrenia appear to be frequently associated with functional impairment of dopaminergic transmission in the prefrontal cortex (Weinberger and Lipska 1995). Thus, enhancement of DA release in this region induced by 5-HT_{2A} or by D_4 receptor blockade may ameliorate negative symptoms by compensating the dopaminergic deficit. However, clinical trials with fananserin, a potent 5-HT_{2A}/DA receptor antagonist, and L745,870, a selective D_4 receptor antagonist, have failed to demonstrate antipsychotic efficacy (Kramer et al. 1997; Truffinet et al. 1999). These findings should be judged with caution since there is no demonstration that these drugs block D_4 receptors in vivo. Moreover, L745,870 has partial agonist properties with a relatively high intrinsic activity (Gazi et al. 1998).

Deficits in cognitive abilities are commonly found in schizophrenia and are usually attributed to frontal lobe dysfunction, probably involving a reduced cortical dopaminergic transmission (Goldman-Rakic and Selemon 1997). Cognitive deficits do not really improve with available antipsychotics (Borison 1996), and it is not yet clear whether drugs blocking 5-HT_{2A}/D_4 receptors are useful. Dopaminergic depletion in prefrontal cortex causes an impairment in spatial working memory (Brozoski et al. 1979; Roberts et al. 1994) and DA release is increased in prefrontal cortex during performance of a test of working memory (Watanabe et al. 1997).

Thus, a drug-induced increase of DA release in the prefrontal cortex may alleviate cognitive deficits associated with frontal-cortical dopaminergic dysfunctions.

A recent study in monkeys found that blockade of D_4 receptors reversed the cognitive deficit caused by the psychomimetic phencyclidine (Jentsch et al. 1999), which is considered a useful model of schizophrenia. It is not known, however, whether increased DA release was involved in this effect.

A deficit in glutamatergic transmission in some parts of the frontal cortex may be responsible for some cognitive deficits in schizophrenic patients (Breier 1999), and blockade of D_4 receptors may indirectly enhance excitatory transmission in cortical pyramidal cells by reducing the activity of inhibitory GABAergic interneurons in cerebral cortex (Mrzljak et al. 1996). The validity of these findings for patients requires appropriate clinical evaluation of the effects of selective D_4 receptor antagonists on cognitive impairments in schizophrenia.

In conclusion, JL13, like other atypical antipsychotics, preferentially increased DA release in the prefrontal cortex. The mechanism of this effect is not clear, but blockade of 5-HT_{2A} receptors may be a major contributing factor. The increased release of cortical DA may alleviate some cognitive deficits associated with reduced dopamine transmission in schizophrenic frontal cortex. The high affinity of JL13 for D_4 receptors may also be a mechanism by which cognitive deficits are improved since preclinical evidence suggests that blockade of these receptors may alleviate some cognitive impairment in proposed models of schizophrenia.

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