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Stimulation of D2 receptors in the prefrontal cortex reduces PCP-induced hyperactivity, acetylcholine release and dopamine metabolism in the nucleus accumbens

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Summary The aim of the present study was to investigate the effects of stimulation of D2 receptors in the prefrontal cortex (PFC) on spontaneous motor activity and the hyperactivity induced by the psychomimetic phencyclidine (PCP). In addition, the effects of prefrontal D2 stimulation under PCP treatment on dialysate concentrations of acetylcholine, choline, dopamine, DOPAC and HVA in the nucleus accumbens were also investigated. Sprague-Dawley male rats were implanted with guide cannulae to perform bilateral injections into the medial PFC of the D2 agonist quinpirole (1.5 and 5 μg/side). Horizontal and vertical spontaneous motor activity and the motor activity induced by systemic injections of the PCP (5 mg/kg i.p.) were monitored in the open field. PFC injections of quinpirole (1.5 and 5 μg/side) significantly decreased horizontal and vertical spontaneous motor activity in a dose-related manner. These effects were blocked by the D2 antagonist raclopride (5 μg/side). Microinjections of quinpirole (1.5 and 5 μg/side) into the PFC also significantly attenuated the hyperactivity produced by PCP (5 mg/kg i.p.). PCP also increased dialysate concentrations of acetylcholine, and dopamine metabolites in the nucleus accumbens. These increases were also reduced by injections of quinpirole (5 μg/side) into the PFC. These results suggest that the stimulation of prefrontal D2 receptors plays an inhibitory role in regulating spontaneous and PCP-induced motor activity and also in the neurochemical changes produced by PCP in the nucleus accumbens.

Keywords: D2 receptors, acetylcholine, dopamine, DOPAC, HVA, prefrontal cortex, nucleus accumbens, motor activity, phencyclidine, schizophrenia, rat

Introduction

Experimental evidence suggests that a functional interaction between the prefrontal cortex (PFC) and the nucleus accumbens exists playing a major role in cognitive and motor behavior (Robbins, 2000; Öngür and Price, 2000; Tzschentke, 2001). In this context, ascending projections to PFC from the mesocortical dopamine pathway have been reported to regulate the activity of the mesolimbic dopaminergic system through descending PFC-nucleus accumbens/VTA projections (Doherty and Gratton, 1996; King et al., 1997; Carr and Sesack, 2000; Del Arco and Mora, 2005). In particular, it has been shown that both stimulation and depletion of dopamine transmission in the PFC changes the release of dopamine in the nucleus accumbens stimulated by stress or amphetamine injections (Doherty and Gratton, 1996; King et al., 1997). This cortico-limbic feedback interaction has been suggested to be involved in locomotion (Kelly and Iversen, 1976; Clarke et al., 1988). In fact, pharmacological studies show that stimulation of dopamine receptors in the PFC exerts an inhibitory action on motor behavior (Vezina et al., 1991; Duvauchelle et al., 1992; Radcliffe and Erwin, 1996; Broersen et al., 1999; Beyer and Steketee, 2000, 2001; Tzschentke, 2001) though the role played by D1 and D2 dopamine receptors has not been fully elucidated. Recently, we have shown that specific stimulation of prefrontal D2 receptors reduces basal extracellular concentrations of dopamine, its metabolites DOPAC and HVA, and acetylcholine in the nucleus accumbens (Del Arco and Mora, 2005). Since changes of dopamine and acetylcholine activity in the nucleus accumbens have been related to motor behavior (Kelly and Iversen, 1976; Ahlenius

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et al., 1987; de Rover et al., 2002), we have suggested an inhibitory role for these receptors in spontaneous motor activity. In line with this suggestion are recent results showing that prefrontal D2 stimulation reduces locomotion induced by cocaine injections (Beyer and Steketee, 2000).

The function of dopamine receptors in the PFC is the focus of intensive research due to their implication in the pathophysiology and treatment of psychiatric disorders such as schizophrenia (Hokfelt et al., 1974; Lidow et al., 1998; Goldman-Rakic et al., 2000; Seamans and Yang, 2004; Miyamoto et al., 2005). In this context, the locomotor hyperactivity induced by the psychomimetic phencyclidine (PCP) in rodents represents a valid experimental model to investigate the cortico-limbic dysfunction that occur in this disorder (Jentsch and Roth, 1999; Takahata and Moghaddam, 2003; Morris et al., 2005). It has been suggested that the effects produced by PCP injections as well as other NMDA antagonists (i.e. ketamine, MK-801) in the PFC underlies the sub-cortical hyperactivity leading to increases of dopamine extracellular concentrations in the nucleus accumbens and hyper-locomotion in rodents (Jentsch et al., 1998; Krystal et al., 2003). Since we have previously shown that the specific stimulation of D2 receptors in the PFC reduces the basal release of dopamine and acetylcholine in the nucleus accumbens (Del Arco and Mora, 2005), it would be of interest to investigate whether direct injections of a D2 like receptor agonist into the PFC also reduces the hyper-locomotion and the release of these same neurotransmitters in the nucleus accumbens, produced by PCP injections.

The aim of the present study was to investigate, by means of local bilateral injections of the D2 like agonist quinpirole, the role of prefrontal D2 dopamine receptors in modulating spontaneous, and PCP-induced motor activity and cholinergic and dopaminergic activity in the nucleus accumbens. More specifically, this study is aimed to investigate first, the effects of stimulation of D2 receptors in the PFC on spontaneous motor activity; and second, the effects of the stimulation of prefrontal D2 receptors on the motor activity induced by acute intraperitoneal injections of PCP (5 mg/kg). Furthermore, the effects of prefrontal D2 stimulation on dialysate concentrations of acetylcholine, choline, dopamine, DOPAC and HVA, in the nucleus accumbens induced by PCP injections were also investigated.

Materials and methods

Animals

The present study was conducted on Sprague Dawley male rats (2–3 months, 250–350 weight). Animals were housed into groups of four in plexiglas cages ($55 \times 35 \times 20$ cm) in temperature controlled rooms (21°C), with a 12-h light/dark cycle and provided with food and water *ad libitum*. Experiments were carried out in accordance with the regulation of both Swedish (CNF, Dnr. S49/01) and Spanish (RD 1201/2005) National Boards for Laboratory Animals.

Microinjections into the prefrontal cortex

Animals were anaesthetised with 1.5% halothane/98.5% air mixture (delivered at 1 ml/min) and stereotaxically implanted in the brain with bilateral guide cannulae to reach the medial prefrontal cortex (mPFC) with the following co-ordinates: +3.2 mm rostral; 0.8 mm medial, from bregma; and −2.5 mm from the top of the skull, with the incisive bar set at −3.3 mm (Paxinos and Watson, 1998). Guide cannulae, 23-gauge stainless-steel (Plastic ONE, USA) were fixed to the skull surface with dental acrylic and two stainless-steel anchorage screws. Dummy cannulae, 28-gauge stainless-steel, were inserted into the guide to keep it clean and prevent occlusion. Six to seven days after surgery, bilateral intra-mPFC injections were performed by means of injection cannulae, 28 gauge stainless-steel, protruding 1.5 mm below the tip of the guide and attached to a micro-pump (CMA microdialysis, Stockholm, Sweden) at a flow rate of 0.4 µl/min. A total volume of 0.5 µl/side was injected (75 s injections) maintaining the injection-cannulae in place for 60 s to allow the diffusion of the drug/vehicle.

The potent D2/D3 agonist (Malmberg and Mohell, 1995) quinpirole hydrochloride (1.5 and 5 µg/side) (Tocris, Cookson, UK) and antagonist raclopride (1.5 and 5 µg/side) (Tocris, Cookson, UK), were freshly dissolved in a modified Ringer solution (1.2 mM $CaCl_2$, 2.7 mM KCl, 148 mM NaCl and 0.85 mM $MgCl_2$; pH 6.0) before local injections in the PFC. These drugs were used in view of the high density of D2 *vs.* the absence of D3 receptors in the rat PFC (Bentivoglio and Morelli, 2005). Phencyclidine (PCP 5 mg/kg i.p.) (SIGMA, Sweden) was injected systemically (1 ml/kg, i.p.). This dose of PCP has been reported to require an intact PFC to produce its effects on motor behavior (Jentsch et al., 1998). Each rat received no more than 4 balanced injections in the PFC with a minimum of 72 h in between injections.

Motor activity

Motor activity experiments were carried out in four automated open field arenas (Del Arco et al., 2004). The open field apparatus consisted of a Plexiglas box ($70 \times 70 \times 45$ cm) equipped with two horizontal rows of eight infrared light sensitive photocell beams located at 5 and 15 cm, respectively, from the basement, allowing the detection of horizontal and vertical (rearing) motor activity. Interruptions of the photocell beams (activity counts) were registered automatically by a regular computer. Spontaneous motor activity: injections were performed into the PFC and then rats were placed immediately in the open field (non-habituated rats). PCP-induced motor activity: PCP intraperitoneal injections were performed after a 60 min habituation period (habituated rats), and immediately after the intra-prefrontal injections. Open field activities were recorded every 5 min during a period of 60 or 120 min, and carried out between 12:00 and 18:00 pm. Rats were placed in the experimental rooms 1 h prior to testing. The arena was wiped with 70% ethanol followed by water between rats.

Microdialysis experiments

All microdialysis experiments were conducted during the dark period of the light/dark cycle [rats were housed under inverted light/dark cycle (lights on/off at 8:00 pm/8:00 am)]. Under Equithesin (2 mg/kg i.p.) anaesthesia rats were stereotaxically implanted with double bilateral guide-cannulae to accommodate microdialysis probes in the nucleus accumbens and to perform microinjections into the mPFC, according to the following co-ordinates from bregma: +3.2 mm rostral; 0.8 mm medial; −2.5 mm from the top

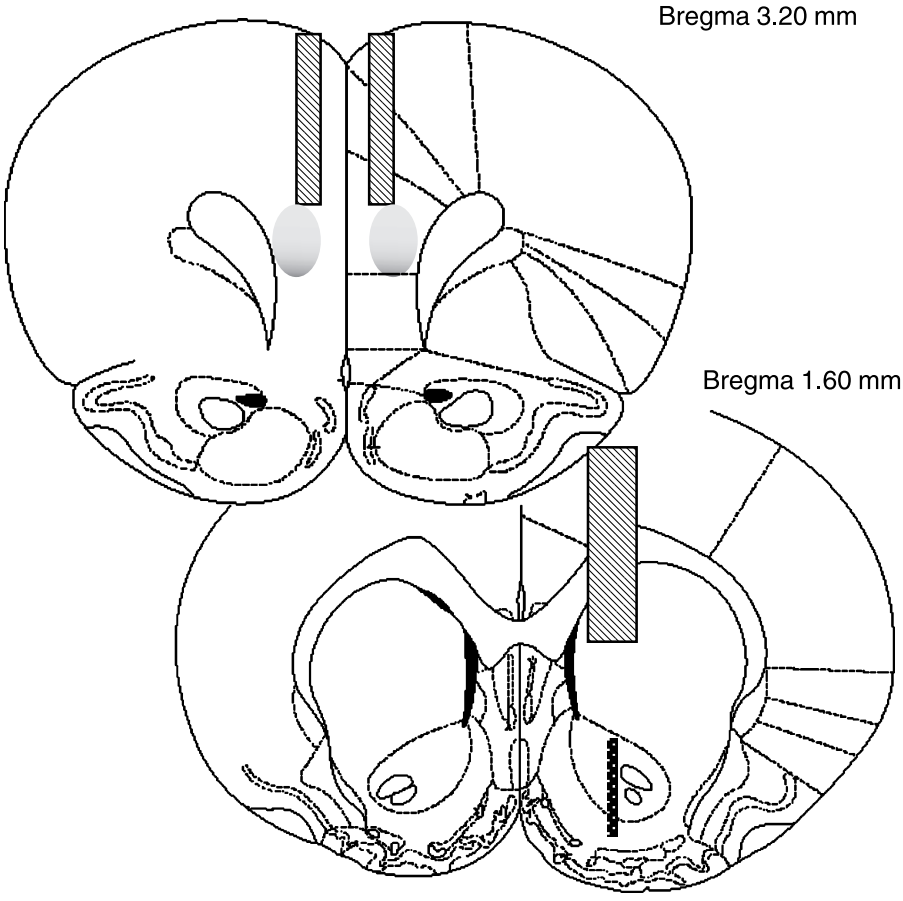

Fig. 1. Schematic representation showing the place where bilateral microinjection cannulae and microdialysis probes were located in the mPFC and nucleus accumbens core, respectively (see co-ordinates in Materials and methods Section) (modified from Paxinos and Watson, 1998)

of the skull for mPFC; and +1.4 mm rostral; +1.6 mm medial; +4.5 mm from the top of the skull for the nucleus accumbens, with the incisive bar set at −3.3 mm (Paxinos and Watson, 1998). Six to seven days after surgery microdialysis experiments were carried out in freely moving animals. Microinjections were performed following the same protocol as described above. Microdialysis probes, constructed in our own workshop, were of concentric design with an active dialysis membrane (5000 Da, Hospal, Barcelona, Spain) of 2 mm in length. The probes were perfused with artificial CSF consisting of (in mM): NaCl 137; $CaCl_2$ 1.2; KCl 3; $MgSO_4$ 1; NaH_2PO_4 0.5; Na_2HPO_4 2; glucose 3; containing the acetyl cholinesterase inhibitor neostigmine 1 μM. pH = 7.3), at a flow rate of 2 μl/min. After basal concentrations of neurotransmitters were established (3 h perfusion period), 20 min samples were collected and immediately stored at −80°C until analyzed. The first three samples were used as a control.

Acetylcholine and dopamine analysis

Acetylcholine and choline, and catecholamines (dopamine and its metabolites DOPAC and HVA) contents of samples were analyzed by reverse-phase HPLC and electrochemical detection (Hernández et al., 2003).

Acetylcholine and choline. Samples were injected in an auto sampler (Hewlett Packard, series 1100, Madrid, Spain) running in a microbore column of 10 μm particles and 530 × 1 mm (Unijet microbore Ach/Ch analytical column. BAS, West Lafayette, IN). The mobile phase consisted of 50 mM phosphate buffer, 0.5 mM EDTA, and ProClin 150 microbiocide Reagent 5 ml/l (BAS), pH = 8.5 adjusted with NaOH 1 N). The mobile phase was not re-circulated and the flow rate maintained at 0.15 ml/min. These conditions allowed Acetylcholine and Choline to be detected at 6.7 and 8.5 min, respectively.

Acetylcholine was hydrolyzed by acetylcholinesterase to choline in a post-column enzyme reactor (Unijet microbore Ach/Ch IMER, BAS); Choline was oxidized by choline oxidase to produce hydrogen peroxide that was detected by an electrochemical detector (Hewlett Packard 1049A, Madrid, Spain) equipped with a platinum electrode at +500 mV. The limit of detection for acetylcholine and choline (8 μl samples) was 5 nM.

Dopamine and metabolites. Samples were injected in a Rheodyne injector (20 μl loop) running in a C18 column of 4 μm particles, and 3.9 × 150 mm (Nova-Pak, Waters, Milford, MA). The mobile phase consisted of 0.1 M acetate-citrate buffer (pH 4.35 adjusted with HCl and NaOH 1 N), 1 mM EDTA, 4.7 mM sodium octyl sulphonate, and 15% methanol. The mobile phase was re-circulated at a flow rate of 1 ml/min. These conditions allowed catecholamines to be detected at the following retention times: 2.1 min DOPAC, 3.7 min HVA, and 5.5 min dopamine.

The compounds were measured by a coulometric detector (Coulochem II model 5200, ESA). Conditioning cell (ESA 5021) was set at 0 mV and analytical cells (ESA 5011) at +275 mV (cell 1) and −250 mV (cell 2). Chromatograms were processed using the Millenium software (Waters). The limit of detection for dopamine (20 μl samples) was 0.15 nanomolar.

Histology

All animals were anaesthetised with an overdose of sodium pentobarbital (120 mg/kg i.p.) and perfused intracardially with 0.9% saline followed by 10% formalin. Bilateral injections into the mPFC of methylene blue were performed just before intracardial perfusions to better visualise the location of injection cannulae. The brain was removed, and the placement of the injection cannulae and/or microdialysis probes was verified in sections cut

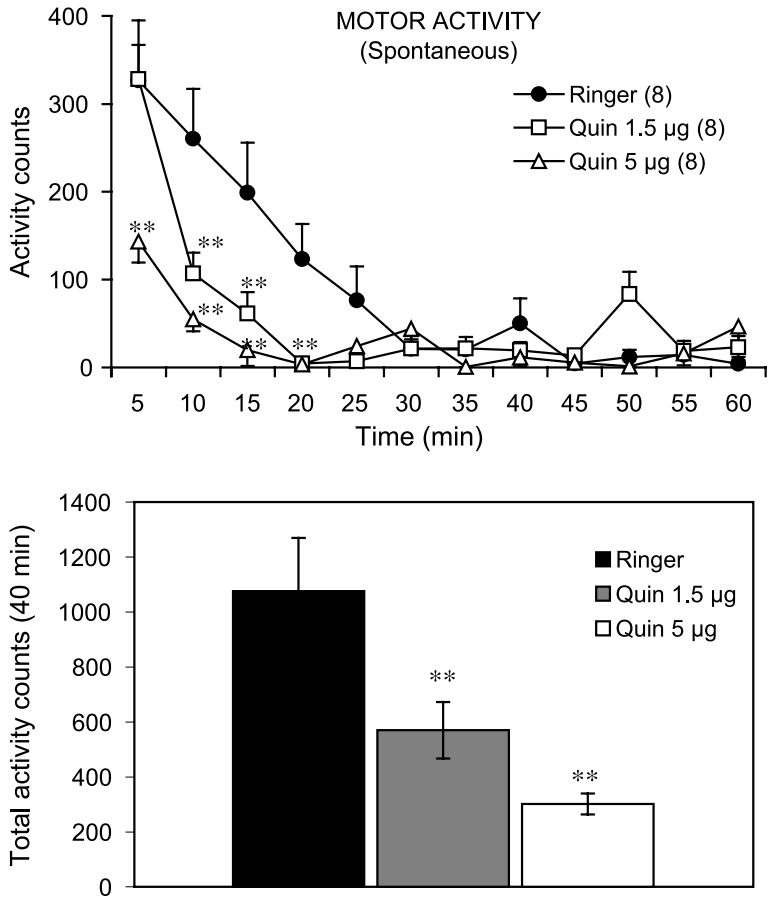

Fig. 2. Effects of injections of the D2 agoist quinpirole into the PFC on spontaneous motor activity in non-habituated rats. Data (mean ± SEM) show activity counts every 5 min (top) or total activity counts (bottom) in the open field. $^{**}p < 0.01$ compared to Ringer after ANOVA (time × treatment) with repeated measures and planned comparisons. Number of animals per group in parentheses

with a cryostat microtome. Animals with incorrect cannulae or microdialysis probe placements were not included in the study.

Statistical analysis

To analyse motor activity counts and dialysate concentrations a two-way analysis of variance (ANOVA) with repeated measures design was used to perform planned comparisons (*a priori* analysis) considering time and drug treatment as within- and between-subject factors, respectively. For the analysis of dialysate concentrations of acetylcholine, dopamine and its metabolites, absolute values were normalised by subtracting basal concentrations (average of three samples values) to each post-basal sample.

Results

Effects of quinpirole injected into the PFC on spontaneous motor activity

The injection of the D2 agonist quinpirole (1.5 and 5 µg/0.5 µl) produced a decrease in spontaneous horizontal [$F(2, 21) = 6.80$, $p = 0.005$] and vertical [$F(2, 21) = 7.26$, $p = 0.004$] motor activity (Fig. 2 and Table 1). The motor activity was inversely correlated with the dose of quinpirole used [horizontal activity: $r = -0.63$, $p < 0.01$; vertical activity: $r = -0.46$, $p < 0.05$]. In particular, quinpirole 1.5 and 5 µg reduced horizontal motor activity (total activity counts during 40 min) to 53% [$F(1, 21) = 7.87$, $p = 0.01$] and to 28% [$F(1, 21) = 18.4$, $p = 0.0003$], respectively, of controls (Ringer). The effects of quinpirole (5 µg) were blocked by the simultaneous injection of the D2/D3 antagonist raclopride (5 µg) [$F(1, 28) = 4.27$, $p = 0.048$]. Raclopride (5 µg) also significantly decreased spontaneous motor activity [$F(1, 20) = 4.45$, $p = 0.047$] (Table 1).

Table 1. *Effects of the injection into the PFC (0.5 µl/side) of the D2 agonist quinpirole and the D2 antagonist raclopride on spontaneous motor activity. Data (mean ± SEM) show total activity counts (40 min). In parenthesis the number of animals*

	Horizontal activity	Vertical activity
Ringer (8)	1077 ± 192	104 ± 23
RACL 1.5 µg (7)	821 ± 80	52 ± 23
RACL 5 µg (8)	672 ± 104**	32 ± 9**
QUIN 1.5 µg (8)	570 ± 103**	25 ± 6**
QUIN 5 µg (8)	301 ± 37**	24 ± 9**
QUIN 5 µg+ RACL 5 µg (8)	655 ± 97**,$	28 ± 5**

* $p < 0.05$, ** $p < 0.01$ compared to ringer, $ $p < 0.05$ compared to quinpirole 5 µg.

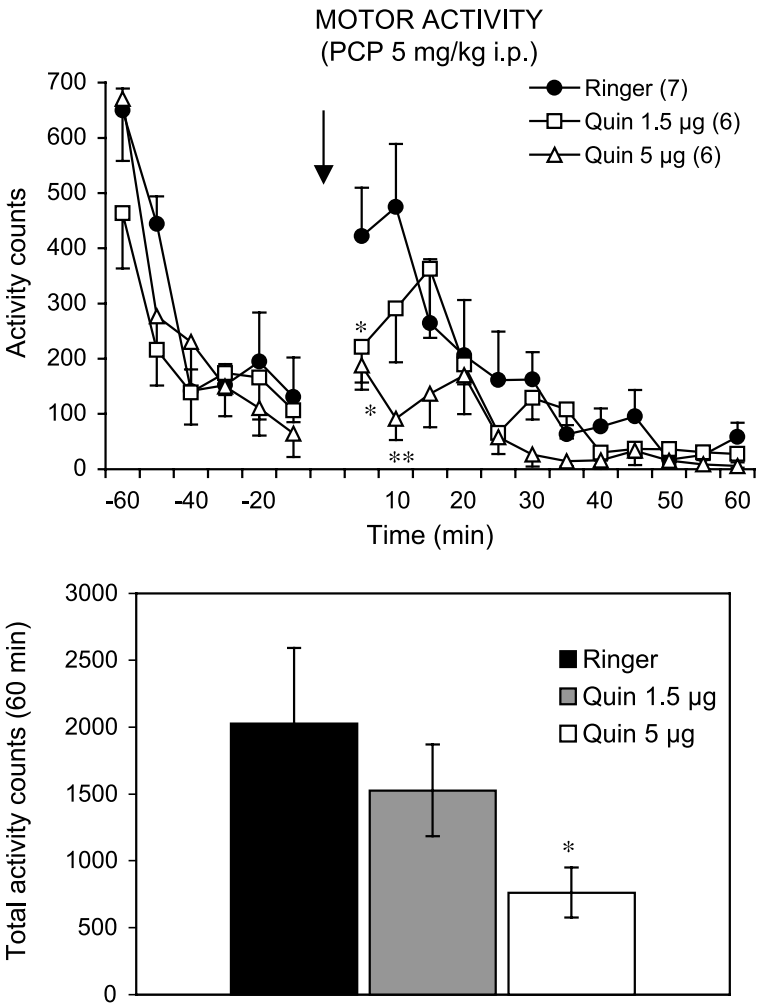

Fig. 3. Effects of injections of the D2 agonist quinpirole into the PFC on PCP-induced motor activity in habituated rats. Arrow indicates injections (intra-prefrontal and systemic). Data (mean ± SEM) show activity counts every 5 min (top) or total activity counts (bottom) in the open field. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to Ringer after ANOVA (time × treatment) with repeated measures and planned comparisons. Number of animals per group in parentheses

Effects of quinpirole injected into the PFC on PCP-induced motor activity

The injection of PCP (5 mg/kg i.p.) produced an increase in horizontal motor activity [$F(11, 176) = 13.95$, $p = 0.0001$]. This increase reached the maximal effect in the Ringer group [360% of control values (control values as the average of 30 min before PCP injections)] (Fig. 3). The injection of quinpirole (1.5 and 5 µg) decreased PCP-induced horizontal motor activity to 75 and 38% [$F(1, 16) = 4.61$, $p = 0.047$] of control values, respectively, (total activity counts for 60 min) (Fig. 3).

Effects of quinpirole injected into the PFC on PCP-induced changes of dialysate concentrations of acetylcholine, choline, dopamine, DOPAC and HVA in the nucleus accumbens

Basal extracellular concentrations in the nucleus accumbens were (mean ± SEM, in nM): 26.1 ± 2 for acetylcholine ($n = 14$); 870.3 ± 132 for choline ($n = 15$); 0.67 ± 0.1 for dopamine ($n = 15$); 567.6 ± 46 for DOPAC ($n = 15$); and 109.0 ± 9 for HVA ($n = 14$). The injection of PCP (5 mg/kg i.p.) produced increases of extracellular concentrations of acetylcholine [$F(1, 12) = 6.06$, $p = 0.029$ (80–120 min)], but not choline, and of the dopamine metabolites DOPAC (though it did not reach statistical significance) and HVA [$F(1, 11) = 5.63$, $p = 0.036$ (120–160 min)], but not of dopamine. The injection of quinpirole (5 µg) into the PFC significantly reduced PCP-induced increases of dialysate concentrations of acetylcholine [$F(1, 12) = 4.77$, $p = 0.049$], DOPAC [$F(1, 12) = 5.16$, $p = 0.042$] and HVA [$F(1, 11) = 4.40$, $p = 0.049$], in the nucleus accumbens (Fig. 4).

Discussion

The present study shows that the injection of the D2 agonist quinpirole into the PFC decreased spontaneous motor

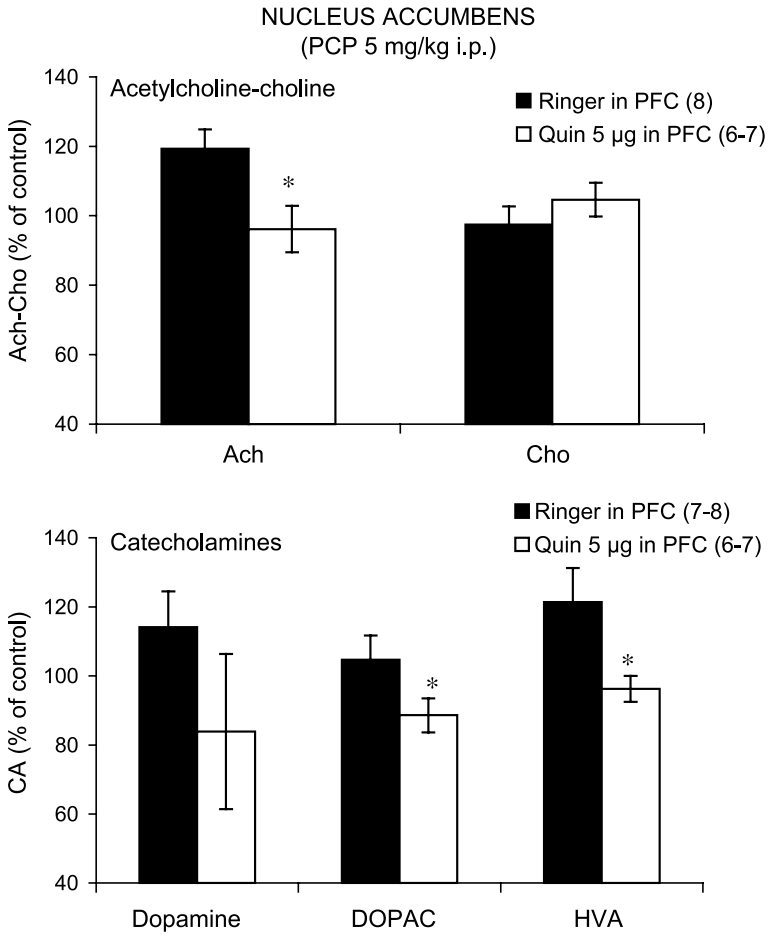

Fig. 4. Effects of injections of the D2 agonist quinpirole into the PFC on PCP-induced changes of dialysate concentrations of acetylcholine, choline, dopamine and the dopamine metabolites DOPAC and HVA in the nucleus accumbens. Data (mean ± SEM) show dialysate concentrations as percentages of basal values after PCP injections (maximun overall effects). Basal values (mean ± SEM, in nM): 26.1 ± 2 for acetylcholine; 870.3 ± 132 for choline; 0.67 ± 0.1 for dopamine; 567.6 ± 46 for DOPAC; and 109.0 ± 9 for HVA. $^{*}p < 0.05$ compared to Ringer in PFC after ANOVA (time × treatment) with repeated measures and planned comparisons. Number of animals per group in parentheses

activity in a dose-dependent manner. These effects were blocked by the prefrontal injection of the D2 antagonist raclopride. Furthermore, the injection of quinpirole into the PFC decreased PCP-induced motor activity in a dose-dependent manner. The prefrontal injection of quinpirole also reduced the increases of dialysate concentrations of acetylcholine, DOPAC and HVA produced by PCP in the nucleus accumbens. These results suggest that the stimulation of prefrontal D2 receptors plays an inhibitory role in modulating spontaneous, and PCP-induced motor activity and cholinergic and dopaminergic activity in the nucleus accumbens.

In vivo studies producing specific lesions of prefrontal dopamine terminals as well as stimulation/blockade of dopamine receptors in the PFC have suggested a role for mesocortical dopamine system in modulating motor activity in the rat (Vezina et al., 1991; Duvauchelle et al., 1992; Radcliffe and Erwin, 1996; Broersen et al., 1999; Tzschentke, 2001). However, the specific role of prefrontal D2 receptors stimulation was not fully elucidated with these studies since the experimental protocols followed and the dopamine agonists/antagonists used (mixed D1–D2) produced contradictory (facilitatory/inhibitory) effects on motor activity (Duvauchelle et al., 1992; Radcliffe and Erwin, 1996; Broersen et al., 1999; Bast et al., 2002; Lacroix et al., 2000). As shown in the results section of this paper, the injection of the D2 agonist quinpirole reduces spontaneous motor activity in a dose-dependent manner. These results are in line with other studies reporting that the stimulation of prefrontal dopamine receptors by mixed agonists (Radcliffe and Erwin, 1996; Broersen et al., 1999) or D2 agonists (Beyer and Steketee, 2000, 2001) reduces spontaneous and/or cocaine-amphetamine-induced locomotion, and further suggest an inhibitory role for prefrontal D2 receptors stimulation in modulating motor behavior.

In support to the involvement of D2 receptors and the effects of quinpirole reducing spontaneous motor activity are the results shown in the present study in which injections of the D2 antagonist raclopride blocked these effects. It should be mentioned that, in line with previous studies (Radcliffe and Erwin, 1996), the blockade of prefrontal D2

receptors also reduced spontaneous motor activity at the highest dose of raclopride used. However, as shown in this report, this effect did not mask the role of raclopride in counteracting the stronger inhibitory effects produced by quinpirole on motor activity. The effects observed with quinpirole and raclopride in the present study parallel other studies reporting similar results in which blockade and stimulation of prefrontal dopamine receptors have similar effects on different behavioural paradigms such as working memory and fear conditioning (Pezze et al., 2003; Goldman-Rakic et al., 2000). Based on these last studies and the results shown here, an inverted U-shape function of prefrontal D2 receptors in regulating spontaneous motor activity can be hypothesized.

The locomotor hyperactivity and the limbic dopaminergic activation produced by the psychomimetic phencyclidine (PCP) in rodents has been used as a valid experimental model to investigate the cortico-limbic dysfunction that occur in schizophrenia (Jentsch et al., 1998; Jentsch and Roth, 1999; Takahata and Moghaddam, 2003). Specifically, some studies have suggested that PCP, as well as other NMDA antagonists, acts at the level of PFC to impair the activity of pyramidal neurons (Shi and Zhang, 2003; Jacksonet al., 2004) and, in turn, the function of the cortico-limbic system and motor behavior. In order to investigate the function of prefrontal D2 receptors in the PFC-nucleus accumbens circuit under PCP treatment, we studied the effects of D2 stimulation in the PFC on PCP-induced locomotion and on the changes in acetylcholine, dopamine and dopamine metabolites extracellular concentrations in the nucleus accumbens. As shown in the results section, PCP increased the extracellular concentrations of acetylcholine and of the dopamine metabolites DOPAC and HVA in the nucleus accumbens as well as locomotion. In contrast to the dopamine metabolites, PCP at the dose used in this study did not increase consistently the extracellular concentrations of dopamine in the nucleus accumbens. Previous microdialysis studies have suggested that higher doses of PCP to the ones used here are in fact needed to better characterize PCP-induced dopamine release in this area of the brain (Schiffer et al., 2001). However, the substantial increases of HVA produced by PCP could be considered to be an index of an increased dopaminergic activity (Deutch et al., 1987; Kashiwa et al., 1995; Del Arco and Mora, 1999). These results are in line with previous studies showing that systemic injections of PCP and other NMDA antagonists produce hyperactivity and increase dialysate concentrations of acetylcholine in PFC (Kim et al., 1999; Nelson et al., 2002) and dopamine, DOPAC and HVA in PFC, nucleus accumbens and/or striatum (Nishijima et al., 1994; Kashiwa et al., 1995; Kato et al., 2000).

As shown in Figs. 3 and 4, stimulation of prefrontal D2 receptors strongly reduced both motor activity and the increases of dialysate concentrations of acetylcholine, DOPAC and HVA in the nucleus accumbens produced by PCP. Given the involvement of acetylcholine, dopamine and nucleus accumbens in motor behavior (Kelly and Iversen, 1976; Ahlenius et al., 1987; de Rover et al., 2002), it is suggested that the blockade of the increases of acetylcholine and dopamine metabolites in the nucleus accumbens produced by prefrontal D2 stimulation underlies, at least in part, the decreases in PCP-induced locomotion observed (but see Takahata and Moghaddam, 2003). These results are in agreement with our own studies in which prefrontal D2 stimulation reduces spontaneous motor activity (present study) and the basal release of acetylcholine and dopamine in the nucleus accumbens (Del Arco and Mora, 2005) and further suggest that this inhibitory action is not changed under the effects produced by PCP.

As shown, the stimulation of prefrontal D2 receptors produces an inhibitory action on hyperactivity induced by acute injections of the psychomimetic PCP. These results are of relevance in the context of the cortico-limbic hyperactivity and the deficient stimulation of prefrontal dopamine receptors, suggested to occur in schizophrenia (Guo-Zhang et al., 2002; Meyer-Lindenberg et al., 2002; Laruelle et al., 2003). Based on the present and previous reports (Tamminga et al., 1978; Dolan et al., 1995), it could be suggested that strategies focused on the specific stimulation of prefrontal D2 receptors would be of interest to consider in order to attenuate the behavioural impairments related to the cortico-limbic dysfunction in schizophrenia (Tamminga and Carlsson, 2002).

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