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Review

Prefrontal cortex–nucleus accumbens interaction: *In vivo* modulation by dopamine and glutamate in the prefrontal cortex

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ABSTRACT

Previous experimental studies have shown that the prefrontal cortex (PFC) regulates the activity of the nucleus accumbens (NAc), and in particular the release of dopamine in this area of the brain. In the present report we review recent microinjections/microdialysis studies from our laboratory on the effects of stimulation/blockade of dopamine and glutamate receptors in the PFC that modulate dopamine, and also acetylcholine release in the NAc. Stimulation of prefrontal D2 dopamine receptors, but not group I mGlu glutamate receptors, reduces the release of dopamine and acetylcholine in the NAc and spontaneous motor activity. This inhibitory role of prefrontal D2 receptors is not changed by acute systemic injections of the NMDA antagonist phencyclidine. On the other hand, the blockade of NMDA receptors in the PFC increases the release of dopamine and acetycholine in the NAc as well as motor activity which suggests that the hypofunction of prefrontal NMDA receptors is able to produce the neurochemical and behavioural changes associated with a dysfunction of the corticolimbic circuit. We suggest here that dopamine and glutamate receptors are, in part, segregated in specific cellular circuits in the PFC. Thus, the stimulation/blockade of these receptors would have a different net impact on PFC output projections to regulate dopamine and acetylcholine release in the NAc and in guided behaviour. Finally, it is speculated that environmental enrichment might produce plastic changes that modify the functional interaction between the PFC and the NAc in both physiological and pathological conditions.

Contents

1. Prefrontal cortex–nucleus accumbens interaction

The prefrontal cortex (PFC) has an essential role in cognition, emotion and reward (Mora and Cobo, 1990; Robbins, 2000; Öngür and Price, 2000; Fuster, 2001; Tzschentke, 2001). Experimental evidence has shown that PFC integrates sensory and limbic (emotional) information and promotes goal-directed behaviours through cortico-

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striatal motor loops (Robbins and Everitt, 1996; Fuster, 1997; Tzschentke and Schmidt, 2000). Relevant in this context are studies showing that PFC regulates the activity of nucleus accumbens (NAc) which is well positioned to function as a limbic–motor interface (Mogenson et al., 1980; Grace et al., 2007). This prefrontal regulation can take place either through the direct excitatory inputs on GABA projecting neurons in the NAc (Sesack and Pickel, 1992; Montaron et al., 1996; Brady and O'Donnell, 2004) or indirectly through the action over other neurons involving different neurotransmitters systems in this same nucleus. In fact, in the NAc, both dopamine inputs arising from the ventral tegmental area (VTA) (mesolimbic dopamine system) (Brady and O'Donnell, 2004; Grace et al., 2007) and cholinergic interneurons (Austin and Kalivas, 1988; de Rover et al., 2002; Pratt and Kelley, 2004) exert a key modulatory action on the activity of GABA output projecting neurons facilitating motor behaviour in response to relevant environmental stimuli. In this context, a dysfunctional regulation of dopamine and possibly acetylcholine release in the NAc by the PFC could underlie, in part, the behavioural abnormalities associated with psychiatric disorders such as schizophrenia (Meyer-Lindenberg et al., 2002).

1.1. Dopamine and acetylcholine in the NAc: modulation by PFC efferent projections

Using different experimental manipulations earlier *in vivo* studies have shown that PFC regulates the release of dopamine in the NAc. In fact, electrical stimulation in the PFC can increase (Taber and Fibiger, 1995; Taber et al., 1995; You et al., 1998; Jackson et al., 2001) and also decrease (Jackson et al., 2001) dopamine release in the NAc. It is of interest at this respect the study by Jackson et al. indicating that the effects on dopamine concentrations in the NAc depend on the frequency of the electrical stimulation applied to the PFC. As a consequence, different PFC efferent pathways might be activated to modulate dopamine release in the NAc (see below). Similarly, 6-OHDA lesions in the PFC have been shown to enhance dopamine release in the NAc produced by high concentrations of K^+ (pressure ejection of K^+ from a pipette) and cocaine or amphetamine intraperitoneal injections (Thompson and Moss, 1995;King et al., 1997;Beyer and Steketee, 1999).

In recent years several immunohistochemical, electrophysiological and neurochemical studies have investigated the anatomical and functional circuitry underlying the modulation of dopamine release in the NAc by PFC efferent projections (see Fig. 1). According to these studies, a glutamatergic pathway from the PFC was proposed to exert a facilitatory effect on dopamine release in the NAc by acting on dopamine cells in the VTA (Murase et al., 1993;Taber et al., 1995). However, this glutamate pathway does not seem to synapse directly on mesolimbic dopamine neurons (Carr and Sesack, 2000). Therefore, an indirect PFC–NAc pathway was proposed involving neurons located in the pedunculo pontine tegmentum (PPT) and/or laterodorsal tegmentum (LDT) which in turn would stimulate dopamine neurons in the VTA projecting to NAc (Fig. 1, no. 5) (Semba and Fibiger, 1992; Forster and Blaha, 2000; Floresco et al., 2003; Omelchenko and Sesack, 2005). Added to that, PFC efferent projections have been also proposed to exert an inhibitory action on dopamine release in the NAc by acting either on GABA interneurons located in the VTA or GABA projecting neurons in the NAc, which in turn would inhibit the activity of dopamine cells in the VTA (Fig. 1, nos. 3 and 4) (Yim and Mogenson, 1980; Overton et al., 1996; Jackson et al., 2001; Sesack and Carr, 2002). Due to the crucial importance to

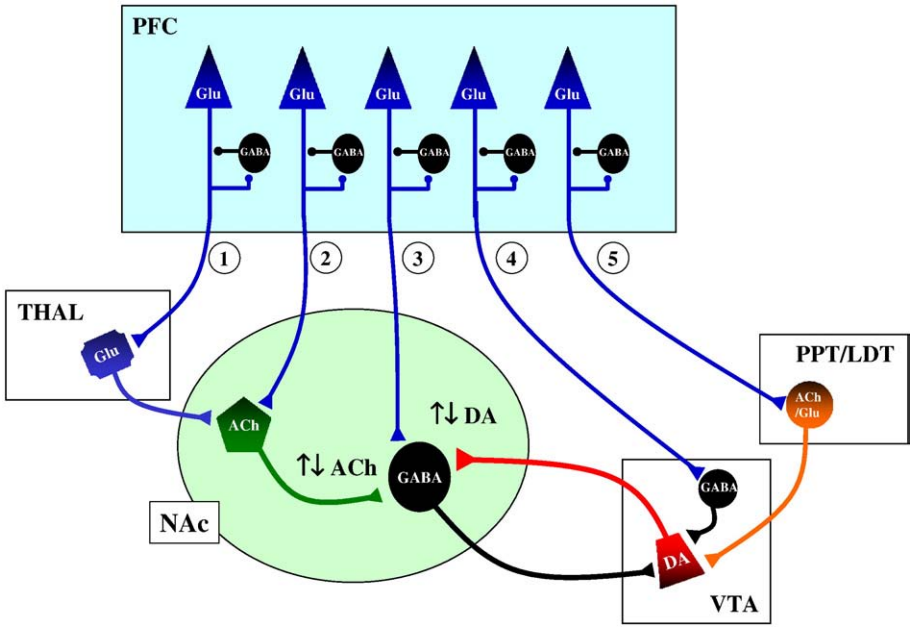

Fig. 1. Schematic diagram proposing the existence of PFC specific circuits (pyramidal neurons–GABA interneurons network), regulated by specific dopamine and glutamate receptors (not represented), and their corresponding direct and indirect outputs (1, 2, 3, 4, 5) to the NAc (see text). According to the results reviewed in the text, the stimulation of prefrontal D2 receptors could reduce the release of acetylcholine in the NAc indirectly by reducing the activity of thalamic inputs to cholinergic interneurons (1) (Meredith and Wouterlood, 1990). The stimulation of prefrontal D2 receptors could also inhibit a direct projection to the NAc (2) (Wilson et al., 1990); but see (Meredith and Wouterlood, 1990). Added to that, the stimulation of prefrontal D2 receptors could reduce the release of dopamine in the NAc by facilitating the activity of efferent projections that in turn inhibit, through GABA neurons, the activity of dopamine cells in the VTA (3, 4) (Yim and Mogenson, 1980; Overton et al., 1996; Jackson et al., 2001; Sesack and Carr, 2002). Alternatively, the stimulation of D2 receptors could reduce the release of dopamine by decreasing the activity of prefrontal efferent projections that facilitate the release of dopamine through PPT/LDT excitatory inputs to VTA (5) (Semba and Fibiger, 1992; Forster and Blaha, 2000; Floresco et al., 2003; Omelchenko and Sesack, 2005). On the other hand, the stimulation of prefrontal group I mGlu receptors could increase acetylcholine release in the NAc by facilitating direct or indirect (through thalamic inputs) glutamate projections to cholinergic interneurons (1, 2). It is also suggested that the specific blockade of NMDA receptors in the PFC could increase the release of both acetylcholine and dopamine in the NAc by increasing the firing rate of pyramidal neurons (Jackson et al., 2004; Homayoun and Moghaddam, 2007) and in turn the activity of PFC efferent projections possibly corresponding to pathways 1/2 and 5. Ach: acetylcholine; DA: dopamine; Glu: glutamate; NAc: nucleus accumbens; PFC: prefrontal cortex; PPT/LDT: pedunculo pontine tegmentum/laterodorsal tegmentum; VTA: ventrotegmental area.

understand the regulation of the mesolimbic dopamine system, intensive research is these days devoted to elucidate the cellular targets as well as the anatomical origin of the different inputs to VTA (Omelchenko and Sesack, 2007; Geisler et al., 2007). There are also studies suggesting a role of glutamate spilling over from glutamate terminals to directly stimulate or inhibit the release of dopamine in the NAc acting on dopamine terminals (Taber and Fibiger, 1995; Segovia et al., 1999). In fact, the existence of an axo-axonic glutamate–dopamine interaction has been supported by immunohistological studies (Sesack et al., 2003). Based on this, we and others have proposed that glutamate can act as a volume transmission signal (Zoli et al., 1998; Del Arco et al., 2003). The role of glutamate receptors regulating the local release of dopamine in the NAc has been recently reviewed by us (Mora et al., 2007b).

Glutamate inputs to the NAc have been described to modulate the activity of cholinergic interneurons in this area of the brain (Meredith, 1999). Thus, direct thalamic inputs (mainly from the paraventricular nucleus) to cholinergic interneurons in the NAc as well as in the striatum have been shown (Meredith and Wouterlood, 1990; Lapper and Bolam, 1992). Indeed, studies showing that electrical stimulation of thalamic nuclei increases the release of acetylcholine in striatum support these anatomical findings (Consolo et al., 1996). No previous studies have investigated the role of PFC regulating the release of acetylcholine in the NAc. However, the release of acetylcholine in striatum has been shown to be regulated by the PFC. In fact, the electrical stimulation of PFC increases the release of acetylcholine in this area of the brain (Taber and Fibiger, 1994; Consolo et al., 1996). According to these last studies, the PFC has been proposed to exert a facilitatory effect on acetylcholine release in the striatum by acting on cholinergic interneurons (Fig. 1, no. 2) (Wilson et al., 1990). Moreover, and since cholinergic interneurons in the NAc receive very little input from PFC (Meredith and Wouterlood, 1990; Lapper and Bolam, 1992) (but see Wilson et al., 1990), it has been proposed (Taber and Fibiger, 1994) an indirect pathway that from the thalamus reaches the NAc (Fig. 1, no. 1) (Hurley et al., 1991; Kelley et al., 2005).

In recent years we are investigating PFC–NAc interaction focused on the modulation of this interaction by dopamine and glutamate in the PFC. Specifically we performed microinjections/microdialysis studies regarding the role of dopamine and glutamate receptors in the PFC on the *in vivo* release of dopamine and acetylcholine in the NAc. In the following sections, results are shown on the effects of stimulation of D2 dopamine and group I mGlu glutamate receptors, and blockade of NMDA glutamate receptors in the PFC, on the release of dopamine and acetylcholine in the NAc and spontaneous motor activity. These results are discussed in the context of the neurochemical and behavioural disturbances associated to the corticolimbic dysfunction suggested to occur in schizophrenia. Added to that and based on our most recent work, it is also speculated in this review that housing animals in an enriched environment can modulate the role of dopamine and glutamate receptors in the PFC to change dopamine and acetylcholine release in the NAc.

2. PFC–NAc interaction: modulation by dopamine and glutamate in the PFC

In the PFC, dopamine varicosities arising from the VTA and glutamate terminals arising from different areas of the brain—hippocampus, thalamus, amygdala and other cortical areas—impinge upon pyramidal glutamatergic neurons and GABA interneurons in the PFC (Peinado and Mora, 1986; Verney et al., 1990; Pirot et al., 1994; Bacon et al., 1996; Carr and Sesack, 1996; Carr et al., 1999; Carr and Sesack, 2000). Different types of dopamine and glutamate receptors are also localized on glutamate pyramidal neurons and GABA interneurons in the PFC (Vincent et al., 1995; Gaspar et al., 1995; Lu et al., 1997; Somogyi et al., 1998). This anatomical arrangement supports the functional interaction between dopamine and glutamate in the PFC previously reported by us and others (see review Del Arco and Mora, 2005).

Several lines of evidence have suggested that dopamine and glutamate in the PFC play a crucial role in the physiology and pathology of this same area of the brain (Hokfelt et al., 1974; Mora et al., 1976; Thierry et al., 1990; Goldman-Rakic et al., 2000; Tzschentke, 2001; Moghaddam, 2002; Sesack et al., 2003; Steketee, 2003; Seamans and Yang, 2004; Castner and Williams, 2007). Since dopamine and glutamate inputs have been shown to modulate the activity of PFC, it has been assumed that both neurotransmitters should also regulate the activity of pyramidal neurons involving direct and indirect descending projections to NAc. However, very few studies have investigated whether dopamine and glutamate receptors in the PFC change the *in vivo* release of dopamine in the NAc. Table 1 shows studies in which using different experimental protocols, and through voltammetry and microdialysis recordings, it is reported that stimulation/blockade of dopamine, glutamate, and also GABA, receptors in the PFC modulates the release of dopamine in the NAc. The role of specific prefrontal dopamine and glutamate receptors, as well as the mechanisms and pathways involved, remain uncertain. No studies so far have investigated the role of these receptors in the PFC modulating acetycholine release in the NAc.

2.1. D2 dopamine receptors in the PFC

We have recently reported that the activation of specific dopamine and glutamate receptors in the PFC changes the release of dopamine and also acetylcholine in the NAc. Specifically, we studied the effects of

Table 1
Summary of some studies showing the effects of different neurotransmitters receptors agonists/antagonists in the PFC on the *in vivo* extracellular concentrations of dopamine in the NAc of the rat brain

PFC manipulation	Dopamine in the NAc	Monitoring technique	Reference
D1+D2 agonists	↔ DA by stress	Voltammetry	Stevenson and Gratton (2003)
D1 antagonists	↑↑ DA by stress	Voltammetry	Doherty and Gratton (1996)
D1 agonists and D2 agonists/antagonists	↔ DA by stress		
D1 agonists	↔ DA	Microdialysis	Olsen and Duvauchelle (2001)
D1 antagonists	↑ DA (24 h post-infusion)		
D2 agonists	↓ DA by cocaine	Microdialysis	Beyer and Steketee (2000)
D1 agonists	↔ DA	Microdialysis	Del Arco and Mora (2005)
D2 agonists	↓ DA (and ACh)		
D2 agonists	↓ DA (and ACh) by PCP	Microdialysis	Del Arco et al. (2007a)
$GABA_B$ agonists	↓ DA by stress	Voltammetry	Doherty and Gratton (1999)
$GABA_B$ antagonists and $GABA_A$ agonists/antagonists	↔ DA by stress		
Glutamate infusions	↑ DA	Voltammetry	Murase et al. (1993)
mGluR2/3 agonists and AMPA antagonists	↑↑ DA by BLA stimulation	Microdialysis	Jackson and Moghaddam (2001)
NMDA antagonists	↑ DA (and ACh)	Microdialysis	Del Arco et al. (in press)

↑↓↔ DA: increases, decreases, no changes basal dopamine; ↑↑ DA: enhances stimulated dopamine; ACh: acetylcholine; BLA: basolateral nucleus of amygdala; PCP: phencyclidine.

D1 and D2 stimulation in the PFC on the extracellular concentrations of dopamine and acetylcholine in the NAc of the awake rat (Del Arco and Mora, 2005). In these studies, bilateral microinjections of the D2 agonist quinpirole, but not the D1 agonist SKF38393, into the PFC reduced the basal extracellular concentrations of dopamine, DOPAC and HVA, and acetylcholine in the NAc (see Fig. 2). The stimulation of prefrontal D2 receptors also reduced spontaneous motor activity of the rats in an open field (Del Arco et al., 2007a). These results are in agreement with others showing a role of prefrontal D2 receptors in inhibiting dopamine release in the NAc (Beyer and Steketee, 2000) and extend them to show an inhibition of acetylcholine release.

The mechanisms and pathways by which stimulation of D2 receptors in the PFC changes the release of dopamine and acetylcholine in the NAc are still uncertain (see Fig. 1). Up to now, many studies have been devoted to investigate the electrophysiological and molecular mechanisms by which dopamine modulates the activity of PFC neurons (Yang et al., 1999; Seamans and Yang, 2004). In particular, the role of D2 stimulation in the PFC neuronal activity is still debated (Sesack and Bunney, 1989; Cepeda et al., 1992; Zheng et al., 1999; González-Burgos et al., 2002; Wang and Goldman-Rakic, 2004; Tseng and O'Donnell, 2004). Previous electrophysiological studies have shown that D2 receptors reduces the activity of pyramidal neurons in the PFC, in part, through GABA interneurons (Pirot et al., 1992; Tseng and O'Donnell, 2007). According to these studies, stimulation of D2 receptors in the PFC could reduce the activity of efferent output projections that facilitate the release of dopamine in the NAc. This would be in line with some *in vivo* studies showing that the perfusion of TTX and $GABA_A$ agonists in the PFC reduces the basal release of dopamine in striatum (Karreman and Moghaddam, 1996; Matsumoto et al., 2003). Alternatively, the stimulation of D2 receptors in the PFC might facilitate the activity of a subset of pyramidal projecting neurons that inhibit dopamine release in the NAc through GABA neurons (Sesack and Carr, 2002; Wang and Goldman-Rakic, 2004). This possibility would agree with other studies showing that the electrical stimulation of PFC reduces dopamine release in the NAc (Jackson et al., 2001) and inhibits dopamine cell activity in the VTA (Overton et al., 1996). Regarding acetylcholine, there are no studies in the literature investigating the role of dopamine in the PFC on the activity of the cholinergic system in the NAc. Stimulation of prefrontal D2 receptors could decrease the release of acetylcholine in the NAc by indirectly reducing the activity of thalamic excitatory inputs to cholinergic interneurons, since a direct prefrontal input to these interneurons in the NAc seems unlikely (Meredith and Wouterlood, 1990). Alternatively and since dopamine has been shown to modulate the release of acetylcholine in the NAc (Keys and Mark, 1998), the possibility exists that the decrease of acetylcholine release is, in part, produced by the parallel decrease of dopamine in this area of the brain.

2.2. Group I mGlu glutamate receptors in the PFC

We also have investigated the effects of stimulating group I glutamate mGlu metabotropic receptors in the PFC on the release of dopamine and acetylcholine in the NAc (Del Arco and Mora, 2005).

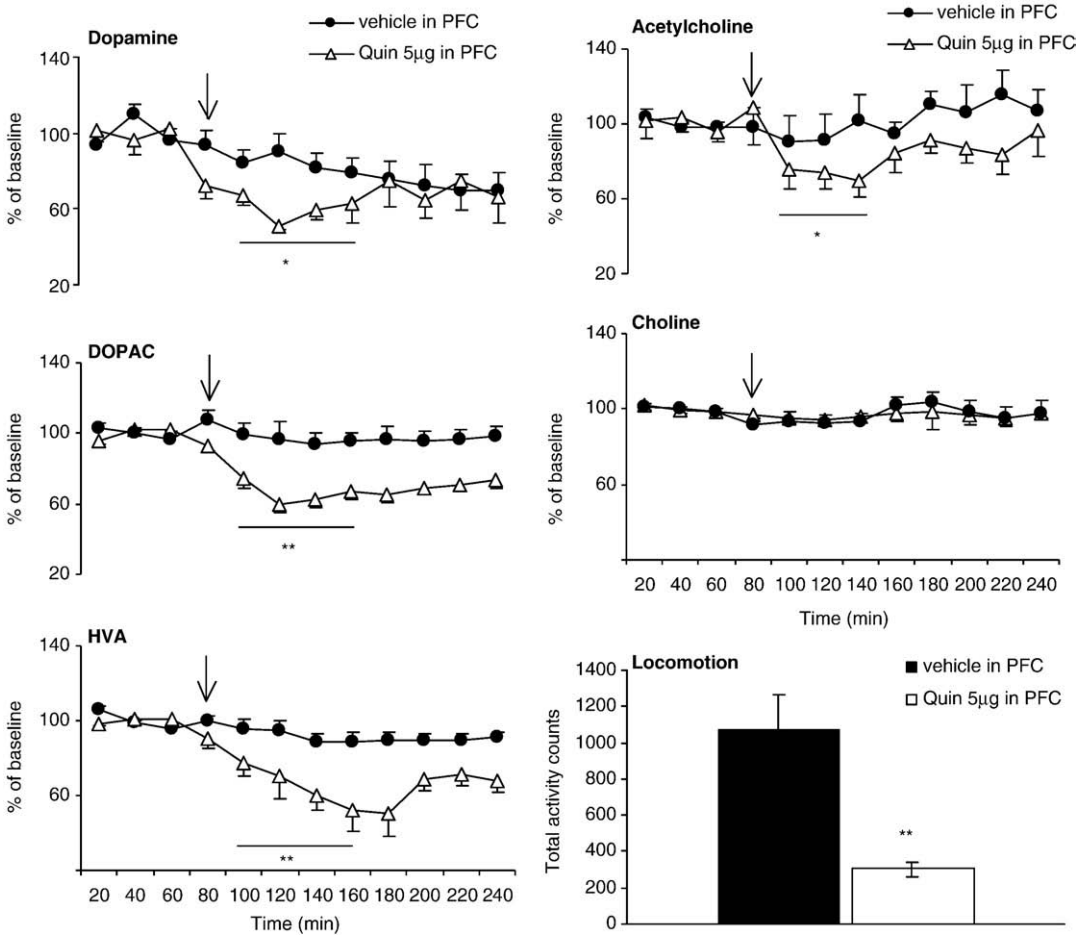

Fig. 2. Effects of bilateral microinjections of the D2 agonist quinpirole in the PFC (arrow) on dialysate concentrations of dopamine, its metabolites DOPAC and HVA, acetylcholine and choline in the NAc of the rat, and on spontaneous motor activity. Data (mean ± SEM) represent the temporal profile as percentages of the baseline (microdialysis) and the total activity counts (40 min) in the open field (locomotion). $^{*}p<0.05$ and $^{**}p<0.01$ vs vehicle group, after two-way ANOVA with repeated measures and planned comparisons (modified from Del Arco and Mora 2005; Del Arco et al., 2007a).

Previous electrophysiological and behavioural studies have suggested that group I mGlu receptors modulate the activity of pyramidal neurons in the PFC and also that these receptors can functionally interact with NMDA receptors to regulate neuronal activity as well as cognitive and motor behaviour (Homayoun et al., 2004; Homayoun and Moghaddam, 2005). However, bilateral microinjections of the group I mGlu agonist DHPG did not change the extracellular concentrations of dopamine, although it did produce a long-lasting increase of acetylcholine, in the NAc. DHPG did not change spontaneous motor activity. These results suggest that group I mGlu receptors in the PFC have a role in regulating acetylcholine transmission, but not dopamine transmission, in the NAc. According to these studies, stimulation of prefrontal group I mGlu receptors could increase the release of acetylcholine in the NAc by facilitating the activity of thalamic inputs to NAc making synaptic contacts with cholinergic interneurons (Meredith and Wouterlood, 1990).

3. PFC–NAc dysfunction: role of dopamine and glutamate receptors in the PFC

A dysfunction of the PFC–NAc interaction has been suggested to be involved in the abnormal cognitive behaviours observed in schizophrenia (Pantelis et al., 1997; Moore et al., 1999; Meyer-Lindenberg et al., 2002). Moreover, an unbalanced interaction between dopamine and glutamate inputs to the PFC could underlie the neurochemical and behavioural disturbances associated with the dysfunction of the PFC–NAc circuit (Carlsson et al., 2001; Goto and O'Donnell, 2004; Yang and Chen, 2005). In this context, it has been postulated that a reduced dopamine activity and the hypofunction of NMDA glutamate receptors in the PFC parallel an excessive dopamine activity in the NAc (Jentsch and Roth, 1999; Tzschentke, 2001; Laruelle et al., 2003; Winterer and Weinberger, 2004; Yang and Chen, 2005). In support of this, studies in laboratory animals have shown that the systemic administration of NMDA antagonists (e.g. phencyclidine, ketamine, MK-801) produces neurochemical and behavioural effects associated with a corticolimbic hyperactivity such as an excessive dopamine release in the NAc and an increased locomotion (Jentsch et al., 1998; Svensson, 2000; Takahata and Moghaddam, 2003). Therefore, the administration of NMDA antagonists has been proposed as a experimental model to investigate the corticolimbic dysfunction associated with schizophrenia (Jentsch and Roth, 1999).

3.1. D2 dopamine receptors in the PFC

For a long time the function of dopamine receptors in the PFC has been the focus of intensive research due to their implications in the pathophysiology and treatment of schizophrenia (Sesack and Bunney, 1989; Cepeda et al., 1992; Yang et al., 1999; Zheng et al., 1999; Abi-Dargham and Moore, 2003; Wang and Goldman-Rakic, 2004; Winterer and Weinberger, 2004; Tseng and O'Donnell, 2004; Trantham-Davidson et al., 2004; Lewis and González-Burgos, 2006). In particular, the function of prefrontal D2 receptors has been suggested to be impaired in schizophrenia (Takahashi et al., 2006). Moreover, according to some studies the dysfunction of D2 receptors in the PFC could be secondary to the hypofunction of NMDA receptors (Laruelle et al., 2003; Wang and Goldman-Rakic, 2004; Aalto et al., 2005).

In previous experiments we had shown an inhibitory role of prefrontal D2 receptors on the release of dopamine and acetylcholine in the NAc. Based on these results, we further investigated whether systemic injections of the NMDA antagonist phencyclidine (PCP) changed the activity of D2 receptors in the PFC of the freely moving rat (Del Arco et al., 2007a). We showed that systemic injections of PCP (5 mg/kg i.p.) produced an increase of the extracellular concentrations of dopamine metabolites, DOPAC and HVA in the NAc, and also an increase in the spontaneous motor activity of the rats. Systemic injections of PCP also increased the extracellular concentrations of acetylcholine in the NAc. Bilateral injections of the D2 agonist quinpirole in the PFC reduced the increases of dopamine metabolites, acetylcholine, and motor activity, produced by PCP in the NAc (see Fig. 3). These results were in agreement with our own previous findings showing the inhibitory action of prefrontal D2 receptors regulating the basal release of dopamine and acetylcholine in the NAc and spontaneous motor activity and further suggested that this inhibitory role of D2 receptors in the PFC is independent on the action of NMDA antagonists. New studies will be needed to elucidate the mechanisms by which quinpirole in the PFC counteracts the effects of systemic injections of PCP. Nonetheless that and based on recent data indicating that NMDA antagonists decrease (Homayoun and Moghaddam, 2007) and D2 agonists increase (Tseng and O'Donnell, 2007) the activity of PFC inhibitory GABA interneurons, quinpirole might be acting directly on these interneurons to counteract the effects of PCP.

3.2. NMDA glutamate receptors in the PFC

Previous studies have suggested that NMDA antagonists such as PCP act at the level of PFC to impair the activity of pyramidal neurons which in turn would alter motor behaviour (Breier et al., 1997; Jentsch et al., 1998; Takahata and Moghaddam, 2003; Krystal et al., 2003). This has been shown in several electrophysiological studies in which

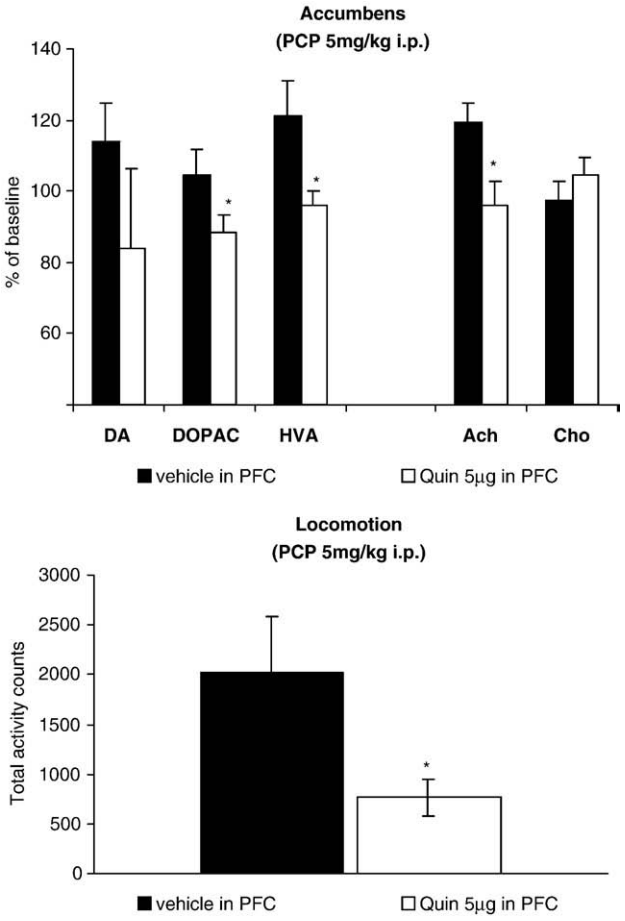

Fig. 3. Effects of bilateral microinjections of the D2 agonist quinpirole in the PFC on dialysate concentrations of dopamine, its metabolites DOPAC and HVA, acetylcholine and choline in the NAc of the rat, and on motor activity, stimulated by systemic injections of the NMDA antagonist phencyclidine (PCP). Data (mean±SEM) represent percentages of baseline and total activity counts (60 min) in the open field (locomotion), after PCP injections. *$p<0.05$ vs vehicle group, after two-way ANOVA with repeated measures and planned comparisons (modified from Del Arco et al., 2007a).

systemic injections of NMDA antagonists increase the firing rate, though decrease the burst firing, of pyramidal neurons in the PFC possibly by reducing the reciprocal inhibition exerted by GABA interneurons (Jackson et al., 2004; Homayoun and Moghaddam, 2007). Based on these findings, it has been proposed that the acute blockade of prefrontal NMDA receptors would increase the activity of PFC glutamatergic efferent projections leading to increases of dopamine and acetylcholine release in the NAc and also to an increase in motor activity (Jentsch et al., 1998; Takahata and Moghaddam, 2003; Yang and Chen, 2005; Del Arco et al., 2007a). These studies however were performed using systemic injections of NMDA antagonists, therefore the specific role of NMDA prefrontal receptors on the release of dopamine and acetylcholine in the NAc remained unclear.

In a series of very recent experiments (Del Arco et al., in press) we showed that bilateral microinjections of the specific NMDA antagonist 3-[(*R*)-2-carboxypiperazin-4-yl]-propyl-1-phophonic acid (CPP) into the PFC, increased the extracellular concentrations of dopamine and its metabolites DOPAC and HVA, and also acetylcholine, in the NAc (see Fig. 4). The injections of CPP also produced motor hyperactivity. These results contrast with the inhibition of dopamine and acetylcholine release produced by the activation of prefrontal D2 receptors, and show that the specific blockade of NMDA receptors in the PFC is able to produce the neurochemical and behavioural changes associated with the dysfunction of the corticolimbic circuit.

According to the above mentioned studies, the prefrontal injections of CPP could facilitate the release of dopamine and acetylcholine in the NAc by stimulating PFC glutamatergic output projections. To investigate the involvement of glutamate receptors in the NAc on the local release of dopamine and acetylcholine produced by prefrontal CPP injections, we perfused NMDA and AMPA/Kainate antagonists through the microdialysis probe into the NAc (Del Arco et al., in press). The blockade of ionotropic receptors in the NAc blunted local acetylcholine increases, but not the increases of DOPAC and HVA. These results suggest that the increased activity of the acetylcholine system, but not that of the dopamine system, in the NAc produced by the specific blockade of NMDA receptors in the PFC, is dependent upon the activation of ionotropic glutamate receptors in the NAc. Previous studies showing that dopamine increases in the NAc by stimulation in the PFC depend on VTA activation, but not on glutamate ionotropic receptors in the NAc, would be in line with these findings (Taber and Fibiger, 1995; Taber et al., 1995). These results further suggest that PFC, at least under the effects of NMDA antagonists, regulate dopamine and acetylcholine release in the NAc through different pathways.

3.3. NMDA–D1 interaction in the PFC

The interaction between specific dopamine and glutamate receptors in the PFC and its role in the behavioural impairments associated with the corticolimbic dysfunctions and schizophrenia has received recently very much attention (Cepeda et al., 1992; Zheng et al., 1999; Seamans and Yang, 2004; Wang and Goldman-Rakic, 2004; Tseng and O'Donnell, 2004; Yang and Chen, 2005). In particular, *in vivo* and *in vitro* studies have shown an interaction between NMDA and D1

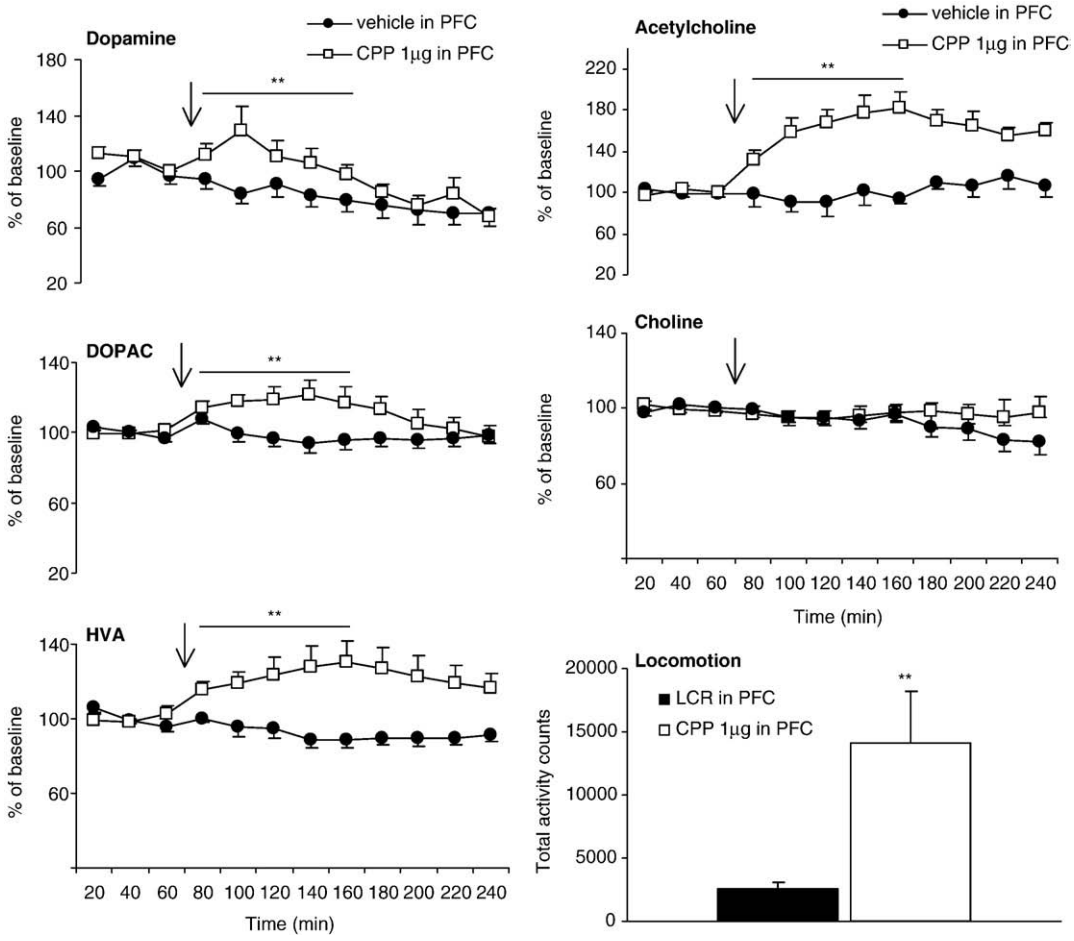

Fig. 4. Effects of bilateral microinjections of the NMDA antagonist CPP in the PFC (arrow) on dialysate concentrations of dopamine, its metabolites DOPAC and HVA, acetylcholine and choline in the NAc of the rat, and on spontaneous motor activity. Data (mean ± SEM) represent the temporal profile as percentages of baseline (microdialysis) and the total distance travelled (120 min) in the open field (locomotion). $^{**}p<0.01$ vs vehicle group, after two-way ANOVA with repeated measures and planned comparisons (modified from Del Arco et al., in press).

receptors at both cellular and behavioural levels. In fact, it has been shown that the activation of D1 receptors increases NMDA-mediated excitability in the PFC through post-synaptic protein kinase A and calcium dependent mechanisms (Tseng and O'Donnell, 2004). Also a coincident activation of NMDA and D1 receptors has been suggested to mediate cognitive and motor behaviour such as working memory and instrumental learning (Baldwin et al., 2002; Castner and Williams, 2007). Based on these studies, it is suggested that the activation of prefrontal D1 receptors could change the neurochemical disturbances associated to schizophrenia through facilitating the activity of NMDA receptors in the PFC and ameliorate the disease (Abi-Dargham and Moore, 2003; Yang and Chen, 2005). According to our own findings, it is hypothesised that the activation of D1 dopamine receptors in the PFC could attenuate the increases of dopamine and acetylcholine release in the NAc, and the motor hyperactivity, produced by the injection of NMDA antagonists in the PFC. Our laboratory is currently investigating this working hypothesis.

4. PFC–NAc interaction and plasticity: environmental enrichment

Environmental enrichment refers to an experimental setting in which groups of animals are housed in large cages containing tunnels, platforms, toys, running wheels that potentiates social interactions, learning and memory and sensory and motor stimulation (Rosenzweig and Bennett, 1996; van Praag et al., 2000; Mohammed et al., 2002; Mora et al., 2007a). Previous studies have shown that housing animals in an enriched environment induces changes in synaptic plasticity, increases the levels of neurotrophic factors, and changes parameters related to different neurotransmitter systems in different areas of the brain such as hippocampus (Rosenzweig and Bennett, 1996; van Praag et al., 2000; Mohammed et al., 2002; Mora et al., 2007a). These findings have provided new perspectives into the mechanisms of environmental dependent plasticity of the brain (van Praag et al., 2000; Nithianantharajah and Hannan, 2006; Mattson and Magnus, 2006).

In recent years, different experimental studies have shown that housing animals in an enriched environment can produce morphological, neurochemical and behavioural changes associated with the PFC–NAc circuit. In fact, it has been shown that animals living in an enriched environment show an increased number of dendritic spines and also a decreased number of dopamine transporters in the PFC (Kolb et al., 2003; Zhu et al., 2005). Environmental enrichment also produces changes in spontaneous and novelty-induced motor activity as well as in behavioural sensitisation to psychostimulants (Bardo et al., 1995; Zimmermann et al., 2001; Schrijver et al., 2002; Larsson et al., 2002; Green et al., 2003). These changes in motor activity have been associated with the faster adaptation to novel situations and the reduced drug abuse vulnerability shown by animals reared in enriched environments (Bardo et al., 2001; Zimmermann et al., 2001; Larsson et al., 2002).

We have recently investigated the effects of an environmental enrichment on the activity of the dopamine and acetylcholine systems in the PFC (Mora et al., 2007a). In particular, we studied in control and enriched animals, the effects of stimulation of D1 receptors in the PFC, by perfusing D1 agonists through the microdialysis probe, on the local release of acetylcholine and on motor activity (Del Arco et al., 2007b). The results showed that the stimulation of prefrontal D1 receptors increased the release of acetylcholine as well as the spontaneous motor activity of the animals and that these increases were lower in animals housed in enriched environment compared to controls. These studies also showed that the number of D1 receptors in the PFC is reduced in enriched animals compared to controls. We have also shown that the release of dopamine and acetylcholine in the PFC produced by an acute mild stress is reduced by environmental enrichment when studied at different groups of age (Segovia et al., 2007a,b; Del Arco et al., 2007c). It is concluded that environmental enrichment down-regulates the activity of the dopamine and acetylcholine systems in the PFC.

According to the data reviewed in this paper the question is raised on whether the plastic changes produced by an environmental enrichment in the PFC will modify the role of prefrontal dopamine and glutamate receptors in modulating dopamine and acetylcholine release in the NAc. For instance, since housing animals in an enriched environment changes the function of D1 receptors in the PFC and D1 receptors have been shown to modulate the activity of NMDA receptors in this area of the brain, it could be hypothesised that the role of prefrontal NMDA, and its interaction, with D1 receptors in modulating dopamine and acetylcholine release in the NAc will be different in enriched animals compared to controls. If this were the case, it would be the first report indicating that the PFC–NAc interaction and its role in physiological and pathological behaviour could be modulated by this environmental manipulation. Interestingly, some studies have suggested that environmental enrichment can attenuate the behavioural abnormalities produced by maternal separation and early isolation, and also associated to models of neurodegenerative disorders (Francis et al., 2002; Hellemans et al., 2004; Paban et al., 2005).

5. Final considerations

Both direct and indirect anatomical pathways are at the basis of the PFC–NAc interaction. Several studies have shown that PFC regulates the activity of the mesolimbic dopamine system. In particular, earlier *in vivo* studies (6-OHDA lesions and electrical stimulation) have shown that PFC regulates dopamine release in the NAc. In the present review, we focused on the specific role of dopamine and glutamate receptors in the PFC that modulate the activity of dopamine, and also acetylcholine, in the NAc. As discussed, the stimulation of D2 receptors in the PFC has an inhibitory role on the release of dopamine and acetiylcholine in the NAc. In contrast the blockade of NMDA receptors in the PFC increases the release of both dopamine and acetylcholine in the NAc. Added to that, the stimulation of group I mGlu receptors in the PFC increases the release of acetylcholine, but not dopamine, in the NAc. All these effects observed in the NAc seem to involve specific PFC efferent projections (see Fig. 1).

Electrophysiological studies have shown that stimulation of dopamine and glutamate receptors in the PFC produces specific changes in the activity of pyramidal neurons (Seamans and Yang, 2004; Tseng and O'Donnell, 2004). In this same area, moreover, the effects of different types of dopamine receptors stimulation seem to be input specific (Zheng et al., 1999; Seamans et al., 2001; Gao and Goldman-Rakic, 2003; Paspalas and Goldman-Rakic, 2005). Thus, for instance, stimulation of D2, but not D1, receptors in the PFC has been shown to attenuate NMDA and AMPA-induced excitation of pyramidal neurons (Tseng and O'Donnell, 2004; Tseng and O'Donnell, 2007) and also enhance non-NMDA-mediated burst firing in a subset of pyramidal neurons (Wang and Goldman-Rakic, 2004). Also, stimulation of D2, but not D1, receptors has been suggested to attenuate the inhibition produced by basolateral amygdala stimulation (Floresco and Tse, 2007) and the excitation produced by hippocampal stimulation (Floresco et al., 2003), on prefrontal pyramidal neurons. Added to that, is the fact that the stimulation of dopamine receptors increase the firing rate of fast spiking GABA interneurons in the PFC (Tseng and O'Donnell, 2007). Precisely this type of GABA interneurons (fast spiking) seems to be specially sensitive to the effects of NMDA antagonists in the PFC (Homayoun and Moghaddam, 2007). According to our results and the above mentioned studies, we hypothesise that different types of dopamine and glutamate receptors are, in part, functionally segregated in specific local cellular networks in the PFC. Thus, the stimulation of these receptors would have a different net impact on the activity of specific PFC efferent projections having a different impact on the function of the NAc (see Fig. 1).

Immunohistochemical studies in which D1 and D2 receptor genes are expressed in different efferent populations in the medial PFC would be in line with this possibility (Gaspar et al., 1995; Lu et al., 1997). Nevertheless, further studies will be needed to substantiate this speculation.

A dysfunction in the PFC–NAc circuit has been involved in the neurochemical and behavioural disturbances associated with psychiatric disorders such as drug addition and schizophrenia (Meyer-Lindenberg et al., 2002; Kalivas et al., 2005). Together with dopamine (Grace et al., 2007), recent studies have suggested that changes of acetylcholine release in the NAc might also play a role in these disorders and therefore in new pharmacological approaches considered in their treatments (Hyde and Crook, 2001; Hikida et al., 2003; Holt et al., 2005). In fact, it has been shown that increases of acetylcholine in the NAc can prevent addictive behaviours (Hikida et al., 2003) and also that stimulation of muscarinic receptors can act as antipsychotic drugs (Shannon et al., 2000). Based on these studies, we suggest that the regulation of NAc dopamine and acetylcholine by dopamine and glutamate specific receptors in the PFC will provide a better understanding on the mechanisms involved in the corticolimbic dysfunction, and possibilities to find new pharmacological strategies to ameliorate symptoms associated with these disorders. Finally, it is speculated that environmental enrichment might produce plastic changes that modify the functional interaction between the PFC and the NAc in both physiological and pathological conditions.

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