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BRAIN RESEARCH

Research Report

Blockade of D1 dopamine receptors in the medial prefrontal cortex attenuates amphetamine- and methamphetamine-induced locomotor activity in the rat

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ABSTRACT

The medial prefrontal cortex (mPFC) is a component of the mesolimbic dopamine (DA) system involved in psychostimulant-induced hyperactivity and previous studies have shown that altering DA transmission or D2 receptors within the mPFC can decrease this stimulant effect. The goal of this study was to investigate a potential modulatory role for D1 receptors in the mPFC in amphetamine (AMPH)- and methamphetamine (METH)-induced hyperactivity. Locomotor activity in an open-field arena was measured in male, Sprague–Dawley rats given an intra-mPFC infusion of vehicle or the D1 receptor antagonist SCH 23390 (0.25 or 1.0 μg) prior to systemic (i.p.) injection of saline, AMPH (1 mg/kg), or METH (1 mg/kg). We found that SCH 23390 produced a dose-dependent decrease in AMPH- and METH-induced locomotion and rearing but had no significant effect on spontaneous behavior that occurred following systemic saline injections. Because SCH 23390 has been shown to have agonist-like properties at 5-HT_{2C} receptors, a follow-up experiment was performed to determine if this contributed to the attenuation of METH-induced activity that we observed. Rats were given intra-mPFC infusions of both SCH 23390 (1.0 μg) and the 5-HT_{2C} antagonist RS 102221 (0.25 μg) prior to METH (1 mg/kg, i.p.). The addition of the 5-HT_{2C} antagonist failed to alter SCH 23390-induced decreases in METH-induced locomotion and rearing; infusion of RS 102221 alone had no significant effects on locomotion and produced a non-significant decrease in rearing. The results of these studies suggest that D1 activation in the mPFC plays a significant role in AMPH- and METH-induced hyperactivity.

1. Introduction

The mesolimbic dopamine (DA) system plays a critical role in psychostimulant-induced locomotor activity. One component of this circuit, the medial prefrontal cortex (mPFC), receives DA input from the ventral tegmental area (VTA) and contains both D1 and D2 receptors. Evidence from several studies suggests that D1 receptors are primarily localized on GABAergic interneurons and, to a lesser degree, on pyramidal excitatory amino acid neurons, whereas D2 receptors tend to be localized primarily on pyramidal cells and to a lesser degree on GABAergic interneurons (Al-Tikriti et al., 1992; Vincent et al.,

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1993; Vincent et al., 1995). There is extensive experimental evidence for the importance of DA transmission within the mPFC in the behavioral response to psychostimulants. For example, amphetamine (AMPH) dose dependently increases extracellular levels of DA within the mPFC (Moghaddam and Bunney, 1989; Maisonneuve et al., 1990). Depletion of mPFC DA via local infusion of the neurotoxin 6-OHDA has been shown to prevent the hyperactivity induced by a single administration of AMPH (Dunnett et al., 1984; Banks and Gratton, 1995; King and Finlay, 1995) as well as the development of behavioral sensitization following repeated exposure to AMPH (Bjijou et al., 2002). These findings are not unequivocal, however, as at least one study demonstrated an increase in the sensitized response to AMPH following mPFC DA depletion (Banks and Gratton, 1995). Furthermore, motor stereotypies induced by relatively high doses of AMPH (2.5–10 mg/kg) are also reported to be increased by these lesions (Carter and Pycock, 1980; Sokolowski and Salamone, 1994; Espejo and Minano, 2001). The reason for these disparate findings is not clear, but one contributing factor may be related to compensatory changes in the function of D1 and D2 DA receptors that occur following lesion-induced depletions of endogenous DA concentrations.

A clear role for DA receptors within the mPFC has been demonstrated in a number of studies that utilized pharmacological manipulations of psychostimulant-induced behavior. For example, intra-mPFC administration of the non-selective D1/D2 antagonist flupentixol decreases acute AMPH-induced locomotion (Bast et al., 2002). Interestingly, intra-mPFC infusion of the selective D2 receptor agonist quinpirole decreases both acute and sensitized cocaine-induced activity (Beyer and Steketee, 2000; Beyer and Steketee, 2002) and prevents expression of neurochemical sensitization by attenuating cocaine-induced increases in DA (Beyer and Steketee, 2002). Lastly, when compared to wild-type controls, D2 receptor knockout mice do not exhibit locomotor stereotypy after repeated injections of a high dose (5 mg/kg) of methamphetamine (METH) (Glickstein and Schmauss, 2004).

In contrast to the number of studies assessing the role of D2 receptor activation in the mPFC in psychostimulant-induced locomotion, considerably less attention has been paid to the role of D1 receptor activation. Thus, the present study examined the contribution of D1 receptor activation in the mPFC to AMPH- and METH-induced locomotor activity. To accomplish this, we recorded open-field behavior in rats given intra-mPFC infusions of the D1 antagonist SCH 23390 just before they received a systemic injection of a dose of AMPH or METH (1 mg/kg, i.p.) that increases locomotion and rearing without producing motor stereotypies (Hall et al., 2008). Because previous studies demonstrated that SCH 23390 has agonist-like effects at 5-HT_{2C} receptors (Briggs et al., 1991) and that this activity is responsible for its ability to decrease 3,4-methylenedioxymethamphetamine (MDMA)-induced activity and locomotor sensitization (Ramos et al., 2005), we also tested the effects of intra-mPFC infusion of the 5-HT_{2C} receptor antagonist RS 102221, alone and in combination with SCH 23390, on METH-induced behavior. These latter experiments were performed only in METH-treated rats since initial examination of METH- and AMPH-induced locomotor activity after infusion of either dose of SCH 23390 revealed no significant between-group differences.

2. Results

2.1. *Effects of SCH 23390 on spontaneous activity*

To determine if intra-mPFC infusions of SCH 23390 altered general motor behavior, spontaneous activity was measured during the first 30 min following infusion of vehicle or SCH 23390 (0.25 or 1.0 μg/side). Fifteen minutes after the infusions, rats were given an i.p. injection of saline. As shown in Fig. 1A, we found no significant effect of infusion on locomotion ($F_{2,60}=1.97$, $p=0.15$). Although SCH 23390 infusions did tend to decrease rearing, particularly at the 1.0-μg/side dose (Fig. 1B), the main effect of infusion was not significant ($F_{2,60}=2.29$, $p=0.11$).

2.2. *Effects of SCH 23390 on AMPH- and METH-induced activity*

On experiment day 2, rats received either SCH 23390 (0.25 or 1.0 μg/side) or vehicle to examine if the indirect activation of D1 receptors by AMPH or METH contributes to the locomotor activation these drugs produce. A two-way ANOVA (drug×infusion) on the locomotion data revealed main effects of infusion ($F_{2,47}=13.69$, $p<0.001$) and drug ($F_{1,47}=5.60$, $p<0.05$) but no drug×infusion interaction ($F_{2,47}=0.12$, $p=0.89$). A dose-

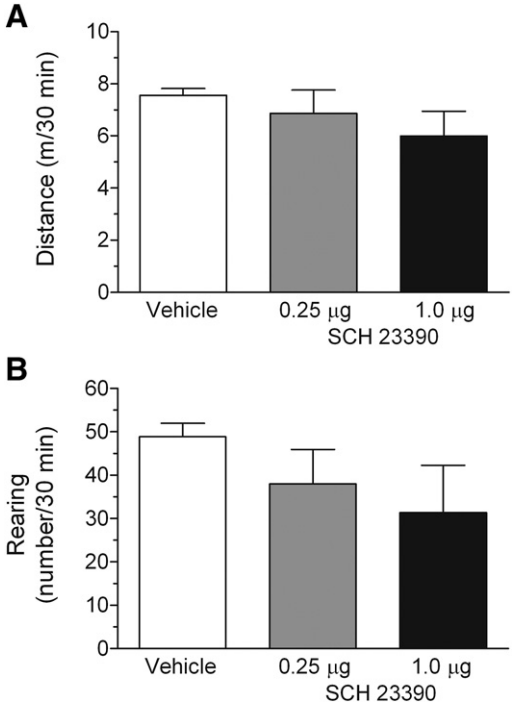

Fig. 1 – Locomotion (A) and rearing (B) in an open-field arena during the 30-min period that followed intra-mPFC infusion of vehicle ($n=48$) or the D_1 antagonist SCH 23390 ($n=6$–7/group) and systemic injection of saline. Data in this and subsequent figures are presented as mean±SEM.