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Research Report

# Amphetamine-induced locomotion, behavioral sensitization to amphetamine, and striatal $D_2$ receptor function in rats with high or low spontaneous exploratory activity: Differences in the role of locus coeruleus

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ARTICLE INFO

*Article history:*
Accepted 31 October 2006
Available online 6 December 2006

*Keywords:*
DSP-4
Amphetamine sensitization
$D_2$ receptor
GTPγS binding
Exploration
Individual differences

ABSTRACT

Individual differences in novelty-related behavior are associated with sensitivity to various neurochemical manipulations. In the present study the amphetamine-induced locomotor activity and behavioral sensitization to amphetamine (0.5 mg/kg) was investigated in rats with high or low spontaneous exploratory activity (HE- and LE-rats, respectively) after partial denervation of the locus coeruleus (LC) projections with a low dose of the selective neurotoxin DSP-4 (*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine; 10 mg/kg). DSP-4 produced a partial depletion (about 30%) of noradrenaline in the frontal cortex of both HE- and LE-rats; additionally the levels of metabolites of dopamine and 5-HT were reduced in the frontal cortex and nucleus accumbens of the LE-rats. Amphetamine-stimulated locomotor activity was attenuated by the DSP-4 pretreatment only in the HE-rats and this effect persisted over repeated testing. Behavioral sensitization to repeated amphetamine was evident only in the LE-rats with intact LC projections. Repeated amphetamine treatment reduced $D_2$ receptor mediated stimulation of [$^{35}$S]GTPγS-binding and dopamine-dependent change in GDP-binding affinity in the striatum, but only in HE-rats. The absence of amphetamine sensitization in HE-rats could thus be related to the downregulation by amphetamine of the G protein stimulation through $D_2$ receptors. Conclusively, acute and sensitized effects of amphetamine depend on the integrity of LC projections but are differently regulated in animals with high or low trait of exploratory activity. These findings have implications to the neurobiology of depression, drug addiction, and attention deficit hyperactivity disorder.



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*Abbreviations:* ANOVA, analysis of variance; DOPAC, dihydroxyphenylacetic acid; DSP-4, *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine; HE, persistently high exploratory activity; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; LC, locus coeruleus; LE, persistently low exploratory activity; VTA, ventral tegmental area; 5-HT, serotonin; [$^{35}$S]GTPγS, [$^{35}$S]-guanosine-5′-(γ-thio)-triphosphate

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doi:10.1016/j.brainres.2006.10.075

## 1. Introduction

Activation of the mesolimbocortical dopamine system is crucial for the expression of the acute behavioral effects of psychostimulants, as well as the induction of behavioral sensitization to amphetamine (Le Moal and Simon, 1991; Vanderschuren and Kalivas, 2000). On acute administration, amphetamine stimulates locomotor activity, and with repeated administration this locomotor response to amphetamine becomes augmented, resulting in behavioral sensitization (Segal and Mandell, 1974; Pierce and Kalivas, 1997). Increase in dopaminergic neurotransmission, particularly in the nucleus accumbens, is also involved in responding to rewarding non-drug stimuli, including novelty (Heffner et al., 1980; Pfaus et al., 1990; Young et al., 1992; Rebec et al., 1997), and has been implicated in the mechanism of action of abused drugs (Di Chiara and Imperato, 1988) and the individual's vulnerability to psychostimulant addiction (Deminiere et al., 1989).

The sensitivity to psychostimulant drugs and the vulnerability to drug abuse seem to be determined, at least in part, by the individual differences in the reactivity to a novel environment (Piazza et al., 1989; Hooks et al., 1991). Several neurochemical features are shown to be associated with individual differences in responding to novel stimuli — compared to low responders to novelty, high responders to novelty have been reported to have higher basal and stimulated dopamine release in the nucleus accumbens (Hooks et al., 1992; Rouge-Pont et al., 1998) and lower serotonin content in the medial prefrontal cortex (Thiel et al., 1999). Rats classified as high responders to novelty tend to be more sensitive to the stimulating and rewarding effects of acute amphetamine administration than low responders to novelty, but this seems to be contingent on the used selection procedures, the doses of amphetamine and the methods for evaluation of the drug effect (Piazza et al., 1989; Hooks et al., 1992; Exner and Clark, 1993; Gingras and Cools, 1997; Klebaur and Bardo, 1999; Klebaur et al., 2001). For example, when an inescapable exploration test is used to assess the animals' reactivity to a novel environment, the high responders to novelty acquire amphetamine self-administration more readily (Piazza et al., 1989) and display higher locomotion to systemic amphetamine administration (0.5–1.0 mg/kg, i.p.) (Hooks et al., 1992). However, Erb and Parker (1994) did not find any correlation between activity in a novel chamber and amphetamine-induced place preference. In contrast, activity in a free-choice novelty test (playground maze) predicted greater amphetamine-conditioned place preference, but not higher locomotion to amphetamine or amphetamine self-administration in the high responders (Klebaur and Bardo, 1999; Klebaur et al., 2001).

The behavioral sensitization to amphetamine also differs in high versus low responders to novelty. The results of the studies investigating this issue are contrasting: Hooks et al. (1992) reported greater sensitization to amphetamine in high responders at least at one dose studied, whereas Piazza et al. (1989) demonstrated behavioral sensitization to amphetamine only in the low responders to novelty. These differences are possibly explained by the differential sensitivity of high and low responding animals to the contextual stimuli during drug administration (Jodogne et al., 1994).

We have used the exploration box test (described in Otter et al., 1997) to measure novelty-related behavior in the rat. This test begins as an emergence test where the animal has a chance to hide in a small chamber or explore an open area with novel objects placed in it, and the animal is thereafter tested repeatedly over consecutive days to observe changes in the balance between the motivations that shape exploratory behavior (Harro, 1993). Starting from the second exposure, rats display individually stable profiles of exploratory behavior in the exploration box. We have recently reported that compromising the noradrenergic projections from the locus coeruleus with a low dose of a selective noradrenergic neurotoxin DSP-4 (10 mg/kg) had differential effects on the amphetamine-induced changes in locomotor activity depending on the animals' spontaneous exploratory activity levels (Alttoa et al., 2005). Specifically, pretreatment with DSP-4 completely abolished the stimulant effect of a single dose of amphetamine in rats classified as high explorers (HE-rats), but did not affect the amphetamine effect in low exploring animals (LE-rats).

The locus coeruleus noradrenergic system has been shown to regulate the activity of the ascending dopamine pathways. Enhanced noradrenaline neurotransmission has been shown to contribute to the acute effects of amphetamine (Vanderschuren et al., 2003). There is a connection of these monoamine systems at the level of the ventral tegmental area where noradrenaline locally either inhibits or excites the dopamine cell bodies (Grenhoff and Svensson, 1993; Grenhoff et al., 1995). The interaction between the LC noradrenergic and the mesotelencephalic dopaminergic systems also operates indirectly via the prefrontal cortex. Dopamine release in the prefrontal cortex is regulated by local noradrenergic nerve terminals (Gresch et al., 1995) and the electrical stimulation of the LC neurons increases both extracellular dopamine and noradrenaline in the prefrontal cortex (Devoto et al., 2005). Further, attenuation of the amphetamine-induced locomotion and dopamine release in the nucleus accumbens has been demonstrated after reduced noradrenergic neurotransmission in the prefrontal cortex (Darracq et al., 1998; Ventura et al., 2003). Activation of the prefrontal alpha-1b-adrenoceptors modulates the acute and sensitized effects of amphetamine, as an acute pharmacological blockade or a genetic knockout of these receptors results in an attenuation of the initial locomotor response to psychostimulants and psychostimulant sensitization (Darracq et al., 1998; Drouin et al., 2002; Weinshenker et al., 2002).

Lesioning the LC projections with DSP-4 decreases basal or stimulated dopamine release in the nucleus accumbens (Lategan et al., 1992; Häidkind et al., 2002). However, in the case of a chronic noradrenaline deficiency, $D_2$ receptors upregulate in response to the reduced dopamine output and the animals become hyperreactive to amphetamine (Harro et al., 2000; Weinshenker et al., 2002; Haile et al., 2003; Harro et al., 2003; Schank et al., 2005). Behavioral studies investigating the effects of the LC lesions on amphetamine-induced changes in behavior have however been inconclusive in determining the role of noradrenaline in psychostimulant effect of amphetamine (Ögren et al., 1983; Archer et al., 1986; Di Lullo and Martin-Iverson, 1991), possibly because of the contribution of the novelty in the experimental situation as large lesions of the LC projections increase neophobia (Harro et al., 1995).