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α_{2A}-Adrenoceptors regulate D-amphetamine-induced hyperactivity and behavioural sensitization in mice

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Abstract

Stimulants, such as D-amphetamine, enhance the release of dopamine in the central nervous system (CNS) and induce locomotor activation in mice. When amphetamine is administered repeatedly, the locomotor activation is progressively increased. This behavioural sensitization may be associated with the development of drug craving, addiction and dependence. Also noradrenergic mechanisms participate in the mediation of the effects of psychostimulants. In this study we show that mice lacking the α_2-adrenoceptor subtype A (α_{2A}-AR knock-out (KO) on C57Bl/6J background) are supersensitive to the acute locomotor effects of D-amphetamine (5 mg/kg) in a novel environment compared to wild-type (WT) control mice. When both genotypes were treated repeatedly with D-amphetamine (2 mg/kg) they developed locomotor hyperactivation (sensitization), but its amplitude was lower in α_{2A}-AR KO mice. Development of hyperactivation was reduced in both genotypes by pretreatment with the selective α_2-adrenoceptor antagonist, atipamezole (1 mg/kg). Acute atipamezole also attenuated the expression of D-amphetamine-induced behavioural sensitization especially in WT mice. Interestingly, α_{2A}-AR KO mice failed to exhibit persistent sensitization after 2 weeks of abstinence from repeated D-amphetamine. Rewarding properties of D-amphetamine, measured by conditioned place preference, were similar in both genotypes. These findings indicate that D-amphetamine-induced acute and sensitized locomotor effects are controlled by α_2-adrenoceptors. Drugs antagonizing the α_{2A}-adrenoceptor subtype may provide a novel approach for reducing drug sensitization and motor complications caused by dopaminergic agents.

Keywords: α_{2A}-adrenoceptor; D-amphetamine; Atipamezole; Locomotor activity; Behavioural sensitization; Knock-out (mouse)

1. Introduction

Dopamine is involved in many behavioural functions, including reward mechanisms, motivation and learning, and control of locomotor activity. The rewarding effects of D-amphetamine-like psychostimulants are believed to be mediated by enhanced dopamine release in the mesolimbic–striatal dopamine system (Wise and Bozarth, 1987). Stimulants induce locomotor hyperactivity in rodents and cause behavioural sensitization after repeated administration (Robinson and Becker, 1986). Sensitization is caused both by enhancement of dopamine release (presynaptic sensitization) and by adaptation of postsynaptic neurons, which become more sensitive to dopamine (Henry and White, 1992). Behavioural sensitization has been suggested to be a useful animal model to investigate the development of drug craving, addiction and dependence in humans (Robinson et al., 1985; Robinson and Berridge, 1993).

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The involvement of the brain noradrenergic system in the behavioural effects of D-amphetamine has been investigated by several groups (Archer et al., 1986; Archer et al., 1985; Juhila et al., 2003; Mohammed et al., 1986; Ogren et al., 1983). Norepinephrine is taken up from the synaptic cleft into presynaptic noradrenergic neurons by the norepinephrine transporter, which is one of the main targets for psychostimulants. Mice genetically lacking norepinephrine transporter were supersensitive to the effects of psychostimulants, and these responses were accompanied by dopamine D_2/D_3 receptor sensitization (Xu et al., 2002). The noradrenergic effects of D-amphetamine-like drugs are partly mediated by α_1-adrenoceptors, since the α_1-adrenoceptor antagonist prazosin reduces D-amphetamine-induced hyperactivity in rats (Blanc et al., 1994; Dickinson et al., 1988). The involvement of α_{1B}-adrenoceptors in control of locomotor and rewarding effects of psychostimulants was recently confirmed in a study on mice lacking this receptor subtype (Drouin et al., 2002). Also the α_2-adrenoceptor antagonists atipamezole atipamezole and idazoxan were found to reduce D-amphetamine-induced behavioural sensitization in mice (Juhila et al., 2003).

α_2-Adrenoceptors mediate a variety of physiological responses and pharmacological effects in the central nervous system (CNS). α_2-AR agonists decrease and antagonists increase norepinephrine release in the CNS via α_2-autoreceptors in noradrenergic cell bodies and nerve endings (Schoffelmeer and Mulder, 1983; Trendelenburg et al., 2001, 1993). α_2-Adrenoceptors are also known to act as heteroreceptors and to regulate the release of other neurotransmitters such as dopamine (Bucheler et al., 2002; Trendelenburg et al., 1994; Whittington et al., 2001; Yavich et al., 1997).

The three α_2-adrenoceptor subtypes, α_{2A}, α_{2B}, and α_{2C}, are widely distributed both in the CNS and in the periphery (McCune et al., 1993; Nicholas et al., 1996, 1993; Scheinin et al., 1994; Wang et al., 1996). The most abundant CNS subtype, α_{2A}-adrenoceptor, is expressed in mice in the locus coeruleus, other brain stem centers, cerebral cortex, hippocampus and spinal cord (Wang et al., 1996). Recent studies on knock-out (KO) mice have confirmed the crucial role of α_{2A}-adrenoceptors in regulation of monoamine release and turnover and in the sedative, analgesic and hypotensive effects of α_2-adrenoceptor agonists (Altman et al., 1999; Ihalainen and Tanila, 2002; Lahdesmaki et al., 2002, 2003; Schramm et al., 2001). The α_{2C}-adrenoceptor subtype is mainly expressed in the mouse striatum, olfactory tubercle, hippocampus and cerebral cortex (Holmberg et al., 2003; Wang et al., 1996). α_{2C}-Adrenoceptor has a role in modulating many aspects of mouse behaviour, such as startle reactivity, aggressive behaviour, amphetamine-induced locomotor hyperactivity, cognitive functions and behavioural despair (Sallinen et al., 1999, 1998a,b, 1997). The expression of α_{2B}-adrenoceptor has not been convincingly demonstrated in the mouse CNS (Bucheler et al., 2002).

We have here assessed the role of α_2-adrenoceptors in D-amphetamine-induced locomotor activation, behavioural sensitization and reward processes. More specifically, we used mice with targeted inactivation of the gene for the α_{2A}-adrenoceptor (α_{2A}-AR KO), and evaluated the effects of acute and repeated D-amphetamine exposure in these mice and their wild-type controls. We also studied the effects of a subtype non-selective α_2-adrenoceptor antagonist, atipamezole, on the responses to D-amphetamine. Atipamezole was chosen to represent this drug class in most of the experiments, because of its high affinity and specificity for α_2-adrenoceptors compared with e.g. yohimbine or idazoxan and various other α_2-adrenoceptor antagonists (Meana et al., 1996; Newman-Tancredi et al., 1998). Atipamezole also has a greater selectivity for α_2- vs. α_1-adrenoceptors than e.g. yohimbine, and it blocks all three α_2-adrenoceptor subtypes with approximately equal potency and penetrates readily into the CNS (Haapalinna et al., 1997; Virtanen, 1989; Virtanen et al., 1989).

2. Materials and methods

2.1. Animals

Experiments were performed with 12- to 20-week-old male mice. The generation of a mouse line with targeted inactivation of the gene encoding the α_{2A}-AR (α_{2A}-AR KO) and its behavioural phenotype has been described previously (Altman et al., 1999; Lahdesmaki et al., 2002). α_{2A}-AR KO mice were backcrossed to C57Bl/6J mice for a minimum of five generations to produce a congenic line. Age-matched wild-type (WT) C57Bl/6J mice of the same genetic background (Jackson Laboratories, Bar Harbor, Maine) were used as control animals. Groups of 10 mice were housed in standard polypropylene cages ($38 \times 22 \times 15$ cm) with free access to standard certified pelleted food (RM1 Maintenance Expanded SQC; Special Diet Services, Essex, UK) and water. Ambient temperature was 22 °C, and a 12:12 h light/dark cycle was maintained with lights on at 6 a.m. All experiments were carried out between 7 a.m. and 5 p.m. All experiments conformed to the European Communities Council Directive 86/609/EEC, and the experiments had approval of the local committee for laboratory animal welfare.

2.2. Drugs

The following compounds were used: D-amphetamine sulphate (Sigma, St. Louis, MO) and atipamezole hydrochloride (Orion Corporation, Orion Pharma, Turku, Finland). Drugs were dissolved in saline (0.9% NaCl) and administered subcutaneously (s.c.) in a volume of 5 ml/kg.

2.3. Open field motility

General activity and stereotypic behaviours were evaluated in a large grey rectangular box ($50 \times 50 \times 25$ cm) and recorded with a video tracking system (Videotrack, Viewpoint, Champagne au Mont D'Or, France). Ambulatory activity was recorded in 5-min periods for 1 h immediately after saline or D-amphetamine (5 mg/kg) administration. Saline or atipamezole (1 mg/kg) was injected 20 min before the challenge. Measured activity parameters were: ambulatory activity, entries into central area (30×30 cm), maximal velocity and inactivity time.