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The influence of ionotropic and metabotropic glutamate receptor ligands on anxiety-like effect of amphetamine withdrawal in rats

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ABSTRACT

Chronic amphetamine use results in anxiety-like states after drug cessation. The aim of the study was to determine a role of ionotropic and metabotropic glutamate receptor ligands in amphetamine-evoked withdrawal anxiety in the elevated plus-maze test in rats. In our study memantine (8 and 12 mg/kg), a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist did not reduce amphetamine withdrawal anxiety. Acamprosate (NMDA and metabotropic glutamate 5 receptor (mGluR5) antagonist) at the dose 200 and 400 mg/kg showed anxiolytic-like effect, thus increasing the percent of time spent in open arms and a number of open arm entries. mGluR5 selective antagonist, MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine hydrochloride) and mGluR2/3 agonist, LY354740 (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid), caused effects similar to acamprosate at doses 1.25–5 mg/kg and 2.5–5 mg/kg, respectively. None of the glutamate ligands influenced locomotor activity of rats when given to the saline-treated group. Taking into account the positive correlation between amphetamine withdrawal-induced anxiety and relapse to amphetamine taking, our results suggest that modulation of mGluRs may prevent relapse to amphetamine and might pose a new direction in amphetamine abuse therapy.

1. Introduction

Amphetamine and other related compounds including methamphetamine, methylphenidate and methylenedioxymethamphetamine are classified as psychostimulants, together with cocaine (Sulzer et al., 2005). Amphetamine and methylphenidate are the most commonly prescribed stimulants for treatment of narcolepsy and attention deficit disorder (Berman et al., 2009). However, amphetamine has a high potential for abuse and is used illicitly by young adults (Teter et al., 2006). Abrupt discontinuation of chronic amphetamine induces a wide spectrum of withdrawal symptoms, including depression and high levels of anxiety (Barr et al., 2002), that have motivational significance and are partially responsible for the maintenance of drug addiction (Koob and Le Moal, 2001).

Amphetamine produces its effects by increasing synaptic levels of the biogenic amines (norepinephrine, dopamine and serotonin), through multiple mechanisms (Fleckenstein et al., 2007; Sulzer et al., 2005), and its behavioral effects such as increased arousal or wakefulness, anorexia, and hyperactivity are elicited predominantly by modulation of dopamine and norephinephrine (Berman et al., 2009). The rewarding/reinforcing effects of amphetamine are mediated via stimulation of the mesocorticolimbic dopamine system (Fleckenstein et al., 2007), although activation of other neurotransmitters, including glutamate (Gass and Olive, 2008), may also be involved. Interestingly, amphetamine is a modulator of D2 dopamine receptors (Amit and Smith, 1992; Fletcher, 1998; Ginovart et al., 1999; Levy et al., 1988; Seeman et al., 2002) and D2 receptors were reported to interact with some of the glutamate receptors (David and Abraini, 2001; Healy and Meador-Woodruff, 1996; Rouillon et al., 2008; Wang et al., 2012). Thus, an interaction between these two systems may have an impact on amphetamine effects.

Published data indicated a central role for glutamate in development and maintenance of addiction to amphetamine and different drugs of abuse (Barr and Markou, 2005; Kalivas, 2009; Olive et al., 2012; Sanacora et al., 2008; Tzschentke and Schmidt, 2003). In vivo microdialysis data reveal that acute amphetamine injection increases extracellular glutamate concentrations (Del Arco et al., 1998; Xue et al., 1996) and prolonged psychostimulant administration induces neuronal adaptations in glutamate function in mesocorticolimbic brain areas (Kalivas, 2007). During drug seeking and craving for amphetamine-like psychostimulants, metabolic activation of corticofugal glutamatergic outputs to the nucleus accumbens and ventral tegmental area occurs (Goldstein and Volkow, 2002). Behavioral data support an increase in glutamatergic activity in the development and expression of amphetamine conditioned hyperactivity and sensitization because drugs that inhibit glutamate receptors

Abbreviations: ANOVA, analysis of variance; GABA, γ-aminobutyric acid; SEM, standard error of the mean; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; iGluRs, ionotropic glutamate receptors; mGluRs, metabotropic glutamate receptors; ip, intraperitoneal injection.

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or decrease glutamate release suppressed these amphetamine effects (Gass and Olive, 2008; Wolf, 1998).

Glutamate signaling occurs through two main classes of receptors: ionotropic (iGluRs) and metabotropic (mGluRs). Currently, only one iGluRs antagonist is used clinically, the rapidly dissociated noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, memantine (1-amino-3,5-dimethyladamantane) (Parsons et al., 2007). This drug was effective in reducing ethanol (Krupitsky et al., 2007) and opiate (Bisaga et al., 2001) withdrawal symptoms in humans. The influence of memantine on psychostimulant-induced withdrawal behavior has not been evaluated yet, although this drug modified reinstatement of cocaine-seeking behavior (Bespalov et al., 2000) and attenuated behavioral sensitization to amphetamine (David et al., 2006).

Recent studies indicated that mGluRs (Nicoletti et al., 2011) have a favorable safety and tolerability profile compared to iGluR ligands (Olive, 2009). The mGluRs are subdivided into three main groups based on their signaling mechanisms and agonist preferences (Conn and Pin, 1997). Postsynaptic mGluRs belonging to group I (mGluR1 and mGluR5) are associated with excitatory functions (Schoepp, 2001). To date, their role in addiction neurobiology, as well as in the anxiety has been well documented (Nicoletti et al., 2011; Olive, 2009). Activation of mGluR5 is inevic for the action of drugs of abuse since deletion of the mGluR5 gene prevents cocaine-induced hyperlocomotion and self-administration (Chiamulera et al., 2001). Consistently with these findings, the mGluR5 antagonists, such as MPEP (6-methyl-2-(phenylethynyl)pyridine and MTEP (3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]pyridine hydrochloride) reduced the acute locomotor stimulant effects of amphetamine (Herzig et al., 2005; Mcgeehan et al., 2004) and amphetamine-conditioned place preference expression in rats (Herzig et al., 2005). Both antagonists, MPEP and MTEP also exhibited anxiolytic-like activity in several models of anxiety in rodents (Busse et al., 2004; Nicoletti et al., 2011; Pietraszek et al., 2005; Spooren et al., 2003).

Acamprosate (calcium acetyl homotaurine) is approved in the pharmacological treatment of alcohol dependence. Although the exact mechanism of action is still unclear, it affects glutamate signaling due to modulatory activity towards NMDA receptors and by an indirect blockade of the mGluR5 (Harris et al., 2002; Witkiewitz et al., 2012). There are several preclinical studies suggesting that acamprosate may be of potential benefit in the treatment of cocaine addiction because it attenuated the development and reinstatement of cocaine conditioned place preference (Mcgeehan and Olive, 2003; 2006) and reduced cocaine- and cue-induced reinstatement of cocaine-seeking behavior in rats (Bowers et al., 2007).

Group II mGluRs are located mainly presynaptically and their major role is to inhibit neurotransmitter release (Nicoletti et al., 2011). They are involved in drug addiction since both mGluR2 and mGluR3, have an established role in synaptic plasticity regulation, and repeated exposure to drugs of abuse alters their function (Nicoletti et al., 2011). LY354740 (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid) is an agonist of mGluR2 and mGluR3. It has been shown that this compound prevented the expression of enhanced amphetamine self-administration in amphetamine-sensitized rats (Kim et al., 2005). It also blocked the expression of locomotor sensitization to amphetamine (Kim and Vezina, 2002). The group II mGluRs (mGluR2 and mGluR3) are also believed to maintain homeostasis in several brain regions related to anxiety (Swanson et al., 2005). Indeed, LY354740 exhibits an anxiolytic activity in several animal and human models of anxiety and its anxiolytic action is comparable to diazepam but causes no learning impairments (for review see Swanson et al., 2005).

Based on the previous research (Vuong et al., 2010), there is an evidence that amphetamine withdrawal can increase anxiety-like behavior in animals. The mGluR5 antagonists and mGluR2/3 agonists have been implicated in the anxiolytic-like behaviors based on pharmacological manipulation. The aim of this study was to compare the influence of group I mGluR antagonist (MTEP) and group II mGluR agonist (LY 354740) with those of acamprosate and memantine on the anxiety-like behaviors during withdrawal from repeated amphetamine in the elevated plus-maze test in rats.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (HZL, Warsaw, Poland; weighing 180–230 g) were used in all experiments. The animals were maintained at standard laboratory conditions (22 °C, 12:12 light–dark cycle) in groups of five rats per cage. The animals were allowed a period of 7 days for acclimation before experiments with access to standard food (Bacutil, Motycz, Poland) and water ad libitum. For all experiments, each animal was used only once. All experimental procedures were performed according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals, and the European Council Directive of 24 November 1986 for the Care and Use of Laboratory Animals (86/609/EEC), and approved by the local Ethics Committee.

2.2. Anxiety-like effect of amphetamine withdrawal

To assess the behavioral changes during amphetamine withdrawal, rats were injected intraperitoneally (ip) with D-amphetamine for 14 consecutive days, once daily at the dose 2.5 mg/kg or with equivalent volume of saline (control group). The regimen of chronic amphetamine administration was based on the procedure of Vuong et al. (2010). All animals had free access to standard food and water during the development of amphetamine dependence. On the 15th day of the experiment, 24 h after the last amphetamine injection, rats were tested for 5 min on the elevated plus-maze during amphetamine withdrawal.

To determine the effects of various glutamate ligands on the anxiety-like behavior during amphetamine withdrawal, the rats that had previously been treated with amphetamine (14 days) received on the 15th day (24 h after the last amphetamine injection): acamprosate (200, 400 mg/kg, ip), memantine (8, 12 mg/kg, ip), MTEP (1.25, 2.5, 5 and 10 mg/kg ip), LY354740 (1.25, 2.5 and 5 mg/kg, ip) or saline before performing the elevated plus-maze test. Furthermore, control (saline) groups received equivalent doses of drugs to evaluate their influence on the behavior in the test.

2.3. Elevated plus maze test

The plus-shaped maze was made of wood and positioned on a height of 50 cm above the floor in a quiet laboratory surrounding. Two opposite arms were open (50 × 10 cm) and the other two were enclosed with walls (50 × 10 × 40 cm). The level of illumination was approximately 100 lx at floor level of the maze. Three days before the experiment, each rat was handled for 5 min every day. The experiment was initiated by placing the rat in the center of the plus-maze facing an open arm, after which the number of entries and time spent in each of the two arms were recorded for a period of 5 min. An “arms entry” was recorded when the rat entered the arm with all four paws. The maze was carefully cleaned with tap water after each test session (Kotlinska and Liljequist, 1998).

The anxiety-like effect of amphetamine withdrawal for each rat was measured as a) the time spent in open arms as a percent of total time spent exploring open and closed arms (Time in open arms) and b) the number of entries into the open arms as a percent of the total number of entries into both open and closed arms (Open arm entries). Furthermore, the locomotor activity of animals was evaluated as the total number of entries into the closed arms of the apparatus.