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COCAINE-INDUCED HYPERACTIVITY IS MORE INFLUENCED BY ADENOSINE RECEPTOR AGONISTS THAN AMPHETAMINE-INDUCED HYPERACTIVITY

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Cocaine-induced hyperactivity is more influenced by adenosine receptor agonists than amphetamine-induced hyperactivity. E. POLESZAK, D. MALEC. Pol. J. Pharmacol., 2002, 54, 359–366.

The influence of adenosine receptor agonists and antagonists on cocaine- and amphetamine-induced hyperactivity was examined in mice. All adenosine receptor agonists significantly decreased the locomotor activity in mice, and the effects were dose-dependent. It seems that adenosine A1 and A2 receptors might be involved in this reaction. Moreover, all adenosine receptor agonists: 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS 21680), A2A receptor agonist, N^6-cyclopentyladenosine (CPA), A1 receptor agonist, and 5'-N-ethylcarboxamidoadenosine (NECA), A2/A1 receptor agonist significantly and dose-dependently decreased cocaine-induced locomotor activity. CPA reduced cocaine action at the doses which, given alone, did not influence motility, while CGS 21680 and NECA decreased the action of cocaine at the doses which, given alone, decreased locomotor activity in animals. These results suggest the involvement of both adenosine receptors in the action of cocaine although agonists of A1 receptors seem to have stronger influence on it. The selective blockade of A2 adenosine receptor by DMPX (3,7-dimethyl-1-propargylxanthine) significantly enhanced cocaine-induced locomotor activity of animals. Caffeine had similar action but the effect was not significant. CPT (8-cyclopentyltheophylline) – A1 receptor antagonist, did not show any influence in this test. Similarly, all adenosine receptor agonists decreased amphetamine-induced hyperactivity, but at the higher doses than those which were active in cocaine-induced hyperactivity. The selective blockade of A2 adenosine receptors (DMPX) and non-selective blockade of adenosine receptors (caffeine) significantly increased the action of amphetamine in the locomotor activity test. Our results have shown that all adenosine receptor agonists (A1 and A2) reduce cocaine- and amphetamine-induced locomotor activity and indicate that cocaine-induced hyperactivity is more influenced by adenosine receptor agonists (particularly A1 receptors) than amphetamine-induced hyperactivity.

Key words: *adenosine, cocaine, amphetamine, locomotor activity*

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INTRODUCTION

Adenosine plays an important role as neuromodulator in the central nervous system (CNS) influencing many behavioral responses [4, 28]. In the CNS, it depresses neuronal activity and causes behavioral depression [31, 39]. Adenosine acts *via* four distinct membrane-bound receptor subtypes: A1, A2A, A2B, A3. [15]. A1 receptors are widely distributed in the brain with high density in the striatum [1]. Functional studies indicate the existence of striatal A1 receptors which modulate dopamine (DA) release [2, 22]. Moreover, A1 receptors have been implicated in the modulation of hippocampal excitability and synaptic processes involved in some types of behavioral learning [30].

In contrast to the widespread distribution of adenosine A1 receptors in the brain, A2A receptors are almost exclusively localized to DA-innervated areas of the CNS, particularly to the striatum, with the highest densities occurring in the caudate-putamen, nucleus accumbens (NAC) and olfactory tubercle [20, 21]. NAC has been implicated in the specific mediation of DA-dependent spontaneous locomotor activity [25, 29]. Thus, A2A adenosine receptors, co-localized with D2 receptors may selectively and potently modulate DA receptor function in the NAC [25], and play the role in the selective modulation of striatal processes involved in the control of locomotor activity and stereotypic behavior [4, 5].

Many studies have shown generalized depressant effects of adenosine and its analogues on locomotor activity [3, 18, 19, 27], and the involvement of A2 receptors in such hypomobility effects has long been postulated [9]. Reduction of motor activity was observed after the stimulation of either A1 or A2 receptors [5, 27]. The local administration of CGS 21680 (A2 adenosine receptor agonist) or raclopride (D2 receptor antagonist) into the NAC reduced dose-dependently spontaneous locomotion in animals [18].

Similarly, adenosine antagonists not only inhibited adenosine analogue-induced psychomotor depressant effects, but, when administered alone, they had some psychomotor stimulant effects [10].

The above findings prompted us to evaluate the influence of adenosine receptor ligands on the action of cocaine and amphetamine, which are indirect DA agonists. Both cocaine and amphetamine increase synaptic levels of DA, potentiate DA neurotransmission in the NAC, and induce marked hyperactivity in animals and humans [8, 42]. In the previous paper [33], we observed that adenosine receptor antagonists markedly and significantly decreased the expression of conditioned place preference (CPP) induced by cocaine in rats, but adenosine receptor agonists diminished it only at lower doses used.

On the basis of the above findings in the present study, we would like to evaluate the influence of adenosine agonists and antagonists on the cocaine-induced locomotor activity in mice. Such experiments have not been performed so far. Moreover, we examined the influence of adenosine receptor agonists and antagonists on amphetamine-induced hyperactivity in mice.

MATERIALS and METHODS

Animals

The experiments were performed on male albino Swiss mice (weighing 17–23 g). The experimental groups consisted of 10 mice. They had free access to food and water and were maintained under 12 h light/dark cycle. The animals were used only once throughout the experiments.

Apparatus and procedure

Locomotor activity was measured in a round actometer cages (32 cm in diameter, two light beams). Each mouse was placed in the cage for 30 min to test its spontaneous activity, 15 min after injection of cocaine and amphetamine and 10 min after injections of adenosine ligands.

Cocaine was used at the following doses: 4 mg/kg – the subthreshold dose, 10 mg/kg – the dose increasing significantly locomotor activity in comparison with the control (0.9% NaCl) group.

Amphetamine was used at the following doses: 1 mg/kg – the subthreshold dose, 5 mg/kg – the dose increasing significantly locomotor activity in comparison with the control (0.9% NaCl) group.

Statistics

The behavioral data were evaluated by a one-way analysis of variance (ANOVA), followed, when appropriate, by individual comparison with the control using Student's *t*-test.

Drugs

The following drugs were used:

Adenosine receptors agonists: 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS 21680), A2A receptor agonist (RBI, USA), N^6-cyclopentyladenosine (CPA), A1 receptor agonist (RBI, USA), 5'-N-ethylcarboxamidoadenosine (NECA), A2/A1 adenosine receptor agonist (RBI, USA).

Adenosine receptors antagonists: caffeine, a nonselective adenosine receptor antagonist (Polfa, Poland), 8-cyclopentyltheophylline (CPT), A1 receptor antagonist (RBI, USA), 3,7-dimethyl-1-propargylxanthine (DMPX), A2 receptor antagonist (RBI, USA).

Dopamine receptor agonists: amphetamine (Sigma, USA), cocaine (Sigma, USA). All drugs were dissolved in saline. Adenosine receptor ligands were administered intraperitoneally, and cocaine and amphetamine were administered subcutaneously. Control animals received the same volumes of saline.

RESULTS

All adenosine receptor agonists significantly decreased the locomotor activity in mice, and the effects were dose-dependent. Namely, CPA (selective A1 receptor agonist) reduced motor activity when it was given alone at doses of 0.1–0.2 mg/kg (Fig. 7). Lower doses of CPA (0.02–0.05) were ineffective (Fig. 1 and 7). CGS 21680 (selective A2A receptor agonist) decreased motor activity of mice dose-dependently at all administered doses (0.01–0.5 mg/kg) (Fig. 2 and 8). Nonselective adenosine receptor agonist NECA did not influence locomotor activity when given at the dose of 0.005 mg/kg, but higher doses (0.01–0.1 mg/kg) dose-dependently diminished motility of mice (Fig. 3 and 9).

All adenosine receptor antagonists: selective A1 receptor antagonist CPT (1 and 3 mg/kg), selective A2 receptor antagonists DMPX (3 and 6 mg/kg) and caffeine nonselective adenosine receptor antagonist (5 and 10 mg/kg) produced not significant effects in this test (Fig. 4–6, 10–12).

Cocaine-induced locomotor activity

Cocaine at 10 mg/kg produced marked hyperactivity in mice. All adenosine receptor agonists: i.e.

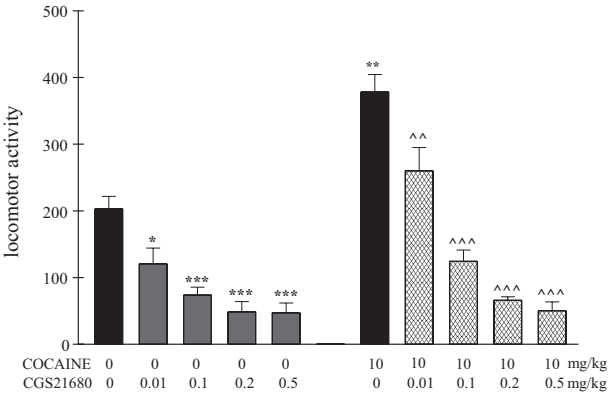

Fig. 2. The influence of CGS 21680 on cocaine-induced hyperactivity. Explanations: 0–0.9%NaCl; * $p < 0.05$ – vs. 0.9% NaCl; ** $p < 0.01$ – vs. 0.9% NaCl; *** $p < 0.001$ – vs. 0.9% NaCl; ^^ $p < 0.01$ – vs. cocaine + 0.9% NaCl; ^^^ $p < 0.001$ – vs. cocaine + 0.9% NaCl

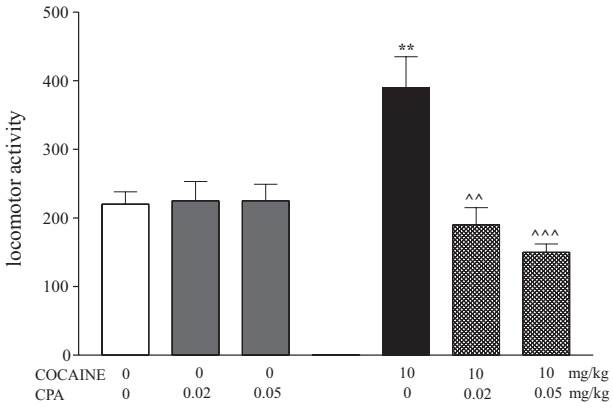

Fig. 1. The influence of CPA on cocaine-induced hyperactivity. Explanations: 0–0.9%NaCl; ** $p < 0.01$ – vs. 0.9% NaCl; ^^ $p < 0.01$ – vs. cocaine + 0.9% NaCl; ^^^ $p < 0.001$ – vs. cocaine + 0.9% NaCl

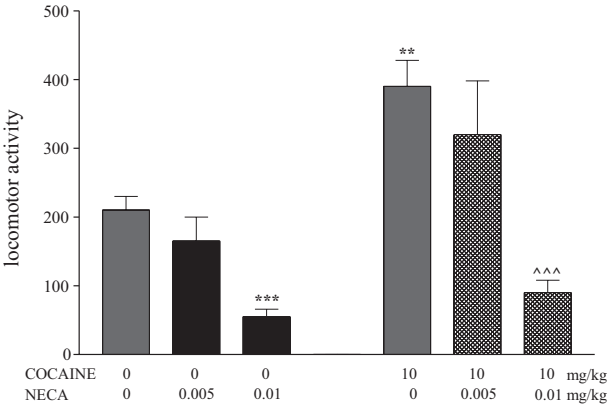

Fig. 3. The influence of NECA on cocaine-induced hyperactivity. Explanations: 0–0.9%NaCl; ** $p < 0.01$ – vs. 0.9% NaCl; *** $p < 0.001$ – vs. 0.9% NaCl; ^^^ $p < 0.001$ – vs. cocaine + 0.9% NaCl

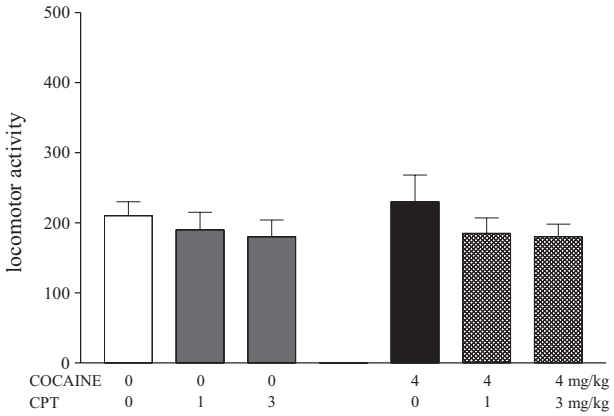

Fig. 4. The influence of CPT on the action of cocaine in the locomotor activity test. Explanations: 0–0.9% NaCl

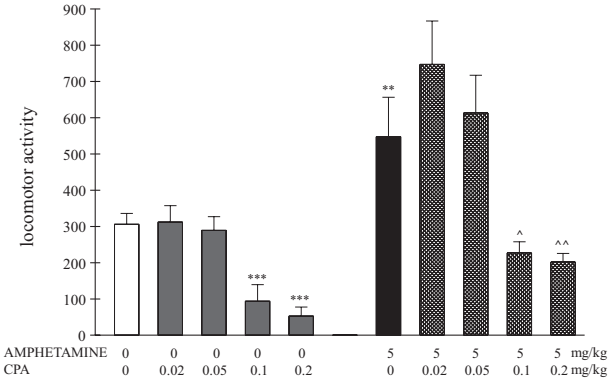

Fig. 7. The influence of CPA on amphetamine-induced hyperactivity. Explanations: 0–0.9%NaCl; ** $p < 0.01$ – vs. 0.9% NaCl; *** $p < 0.001$ – vs. 0.9% NaCl; ^ $p < 0.05$ – vs. amphetamine + 0.9% NaCl; ^^ $p < 0.01$ – vs. amphetamine + 0.9% NaCl

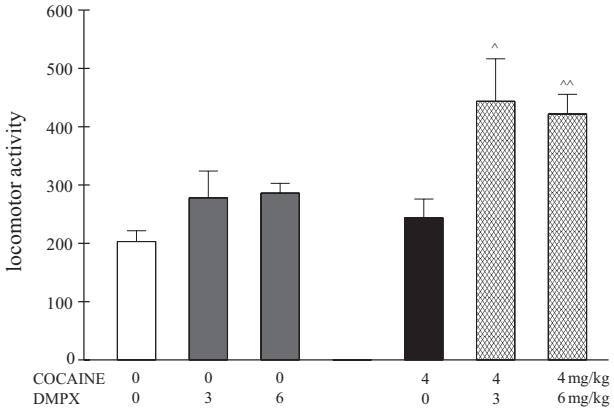

Fig. 5. The influence of DMPX on the action of cocaine in the locomotor activity test. Explanations: 0–0.9%NaCl; ^ $p < 0.05$ – vs. cocaine + 0.9% NaCl; ^^ $p < 0.01$ – vs. cocaine + 0.9% NaCl

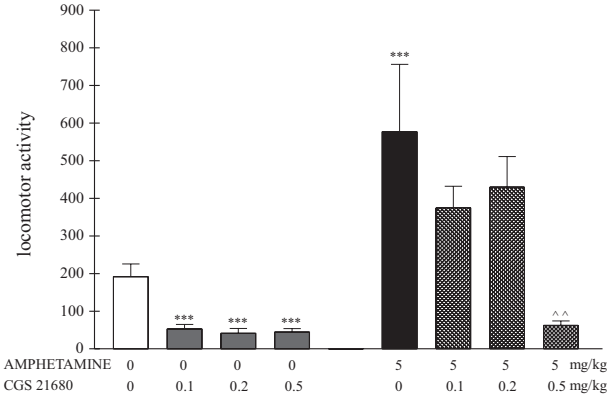

Fig. 8. The influence of CGS 21680 on amphetamine-induced hyperactivity. Explanations: 0–0.9%NaCl; *** $p < 0.001$ – vs. 0.9% NaCl; ^^ $p < 0.01$ – vs. amphetamine + 0.9% NaCl

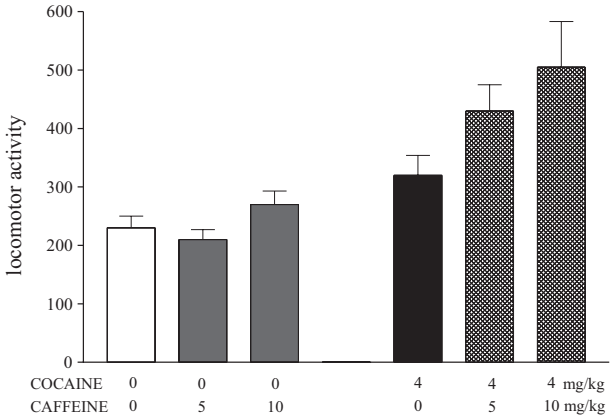

Fig. 6. The influence of caffeine on the action of cocaine in the locomotor activity test. Explanations: 0–0.9% NaCl

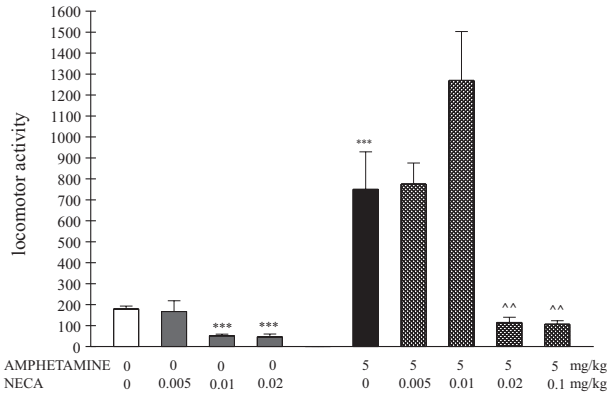

Fig. 9. The influence of NECA on amphetamine-induced hyperactivity. Explanations: 0–0.9% NaCl; *** $p < 0.001$ – vs. 0.9% NaCl; ^^ $p < 0.01$ – vs. amphetamine + 0.9% NaCl

CPA (0.02–0.05 mg/kg), CGS 21680 (0.01–0.5 mg/kg) and NECA (0.005–0.01 mg/kg) dose-dependently reduced this effect of cocaine (Fig. 1–3).

Cocaine at 4 mg/kg did not change motility of mice, and CPT did not show any influence on it (Fig. 4). However, selective blockade of A2 adenosine receptor by DMPX significantly enhanced cocaine-induced motor activity of animals (Fig. 5). Caffeine (5–10 mg/kg) had similar action but the effect was not significant (Fig. 6).

Amphetamine-induced locomotor activity

Amphetamine at 5 mg/kg produced marked hyperactivity in mice. All adenosine receptor agonists: i.e. CPA at doses of 0.1 and 0.2 mg/kg, CGS 21680 (0.5 mg/kg) and NECA (0.02–0.1 mg/kg) significantly and dose-dependently decreased amphetamine-induced hyperactivity (Fig. 7–9).

Amphetamine at 1 mg/kg did not change motility of mice (Fig. 10–12). The selective blockade of A2 adenosine receptors (DMPX) and non-selective blockade of adenosine receptors (caffeine) significantly increased the action of amphetamine in the locomotor activity test (Fig. 11, 12). CPT did not influence the action of amphetamine in this test (Fig. 10).

The analyses of variance applied to the effects of CGS 21680 on the cocaine- and amphetamine-induced hyperactivity, respectively, showed following effects ($F_{9, 66}$: 31.68 $p < 0.0001$ and $F_{7, 40}$: 7.349 $p < 0.0001$); the effects of NECA ($F_{5, 33}$: 7.810 $p < 0.0001$ and $F_{8, 45}$: 15.399 $p < 0.0001$); the effects of CPA ($F_{5, 33}$: 8.025 $p < 0.0001$ and $F_{9, 59}$: 9.704 $p < 0.0001$); the effects of DMPX ($F_{5, 42}$: 5.581 $p = 0.0005$ and $F_{6, 35}$: 3.693 $p = 0.006$); the effects of CPA ($F_{5, 32}$: 0.864 $p = 0.518$ and $F_{6, 35}$: 2.068 $p = 0.082$); the effects of caffeine ($F_{5, 36}$: 5.54 $p = 0.0007$ and $F_{5, 39}$: 3.331 $p = 0.013$).

DISCUSSION

NAC, is a part of the ventral striatum involved in the control of locomotor activity [41]. It appears to specifically mediate DA-dependent spontaneous and psychostimulant-induced locomotion *via* the accumbal-pallidal projection [40]. The adenosine A2A receptors are abundantly expressed in the NAC and in the caudate-putamen [20, 38], modulating striatal dopaminergic neurotransmission. They are co-localized with D2 receptors on strio-

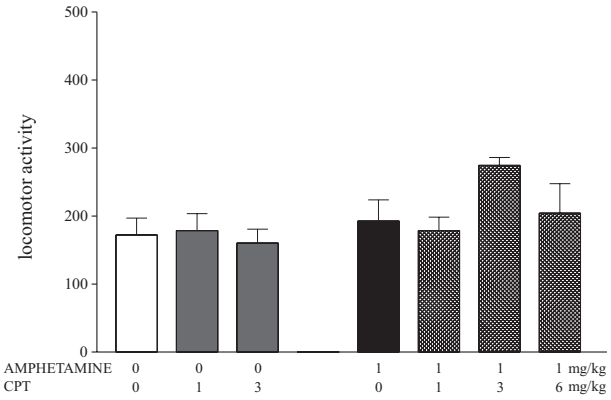

Fig. 10. The influence of CPT on amphetamine-induced locomotor activity. Explanations: 0–0.9%NaCl

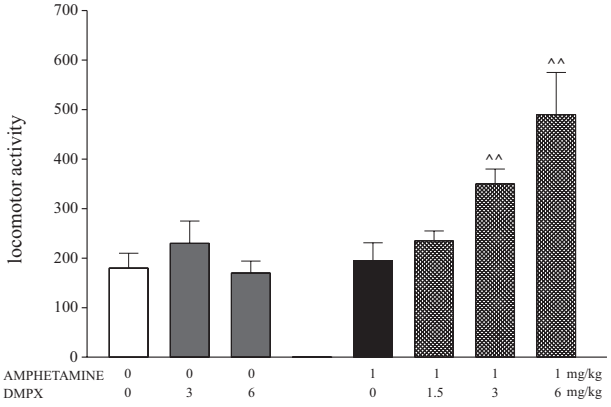

Fig. 11. The influence of DMPX on amphetamine-induced locomotor activity. Explanations: 0–0.9%NaCl; ^^ $p < 0.01$ – vs. amphetamine + 0.9% NaCl

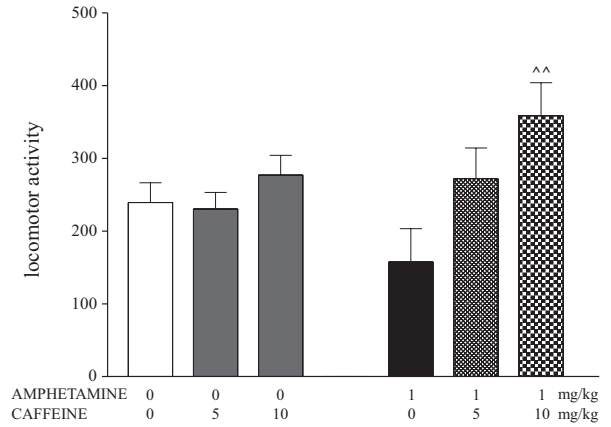

Fig. 12. The influence of caffeine on amphetamine-induced locomotor activity. Explanations: 0–0.9%NaCl; ^^ $p < 0.01$ – vs. amphetamine + 0.9% NaCl

pallidal neurons, while adenosine A1 receptors are found on GABAergic neurons (strionigral and strioentopeduncular neurons) with D1 receptors. Therefore, a strong antagonistic interaction between adenosine and DA seems to exist in the striatum [10–12].

Cocaine and amphetamine are potent psychostimulants and both potentiate DA neurotransmission in the NAC [42]

In our study, cocaine-induced locomotor hyperactivity was significantly and dose-dependently decreased by all adenosine receptor agonists, and selective adenosine A1 agonist CPA reduced cocaine action at the low doses (0.02–0.05 mg/kg), which, given alone, did not influence motility. Perhaps this action is linked with the inhibition of neurotransmitter release by A1 agonists [11, 12], because it was shown that the activation of striatal adenosine A1 receptors could block the release of DA [2, 22]. Selective A2A adenosine receptor agonist CGS 21680 and adenosine A2/A1 receptor agonist NECA decreased the action of cocaine at the doses, which, given alone, decreased locomotor activity in animals. These action of CGS 21680 and NECA is probably linked with the antagonistic interaction between A2 and D2 receptors [10, 16]. Among adenosine receptor antagonists, A2 receptor blocker DMPX significantly enhanced cocaine-induced motility of mice in the present studies. Caffeine had similar action but the effect was not significant. Thus, these results suggest the involvement of both adenosine receptors in the action of cocaine although agonists of A1 receptors seem to have stronger influence on it. These results confirm the existence of a specific antagonistic interaction between adenosine and DA receptors in the basal ganglia. This interactions between adenosine A2A and D2 receptors has been well characterized at the behavioral, functional and biochemical levels [10, 11, 16]. Another specific antagonistic interaction between A1 and D1 receptors has also been documented, for example: adenosine A1 agonist – CPA was found to selectively counteract some behavioral effects of the DA D1 agonist SKF-38393 [12], A1 antagonist (8-cyclopentyl-1.3-dimethylxanthine) significantly potentiated it [34], and the stimulation of adenosine A1 receptors modified the binding characteristics of DA D1 receptors in the NAC and in the medial prefrontal cortex, the brain areas, which contain both types of receptors [13]. Our results concerning decreasing influence of CPA on cocaine-induced hyperactivity seem to support the existence of this A1-D1 antagonistic interaction. Moreover, Cabib et al. [6] have shown that the locomotor hyperactivity induced by cocaine can be blocked by the D1 receptor antagonist SCH 23390 at the doses ineffective when given alone, but haloperidol and metoclopramid (D2 receptor antagonists) might prevent cocaine-induced hyperactivity at high, hypokinetic doses [6]. Thus, D1 receptors seem to play a basic and necessary but not sufficient role in cocaine-induced hyperactivity in mice [6, 7]. Cocaine is an indirect DA agonist, thus, it is conceivable that its effects are dependent on the activation of both D1 and D2 receptors. Hence, the above our observations suggest that the action of cocaine may also be influenced by both adenosine receptors, although A1 adenosine receptors seem to be more involved.

The psychostimulant amphetamine activates the forebrain dopaminergic systems by enhancing DA release from presynaptic terminals, therby producing hyperlocomotion [14]. The studies concerning interaction between adenosine receptor ligands and amphetamine or other dopaminergic stimulants were performed by other authors, for example, it has been shown [11, 12] that low doses of A1 and A2A receptor agonists selectively counteract the motor activating effects induced by D1 and D2 receptor agonists, respectively [11, 12, 35, 36].

In the present study, the amphetamine-induced hyperactivity (5 mg/kg) was enhanced by adenosine receptor antagonists (DMPX and caffeine) similarly as cocaine hyperactivity. However, the effect of amphetamine was decreased by adenosine receptor agonists given at the higher doses than those which were active in cocaine-induced hyperactivity. CPA, CGS 21680-50 and NECA doses required to lower amphetamine-induced hyperactivity were 5-, 50-, and 2-fold higher, respectively, than doses reducing cocaine action in this test.

Thus, our experiments with locomotor activity have shown some quantitative differences between the reactivity of adenosine ligands on the action of cocaine and amphetamine. These differences are the result of its mechanisms of action. Both psychostimulants increase synaptic levels of DA and potentiate DA neurotransmission in the NAC [8, 42]. However, the molecular bases of actions of these drugs are not identical. Whereas they both block DA uptake through the binding to the DA transporter [23, 24, 32, 37], amphetamine also in-

duces DA release [23]. Xu et al. [43] reported that the D1 receptor is essential for mediating the acute cocaine-induced locomotor responses and stereotyped behavior in mice. In the further experiments, these authors [42] have shown that D1 receptor also participates in behavioral responses induced by amphetamine. Graybiel et al. [17] have shown that cocaine and amphetamine differently induce drug-specific activation of the *c-fos* gene expression in subdivisions of the striatum, and they suggested that different parts of the striatum might contribute to the functional differences between these psychostimulants. For example, distinct accumbal subareas are involved in place conditioning of amphetamine and cocaine: significant CPP was observed with amphetamine infused into the core area but cocaine infused into the shell area [26]. Thus, quantitative differences observed between cocaine- and amphetamine-induced locomotor effects in our study may be caused by these anatomical distinctions.

Summing up, our results have shown that all adenosine receptor agonists (A1 and A2) reduced cocaine- and amphetamine-induced locomotor activity and indicate that cocaine-induced hyperactivity is more influenced by adenosine receptor agonists (particularly of A1 receptors) than amphetamine-induced hyperactivity.

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