



## Involvement of adenosine receptors in dizocilpine-induced motor activity in mice

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### Abstract:

The effect of adenosine receptor ligands on dizocilpine-induced locomotion was studied in mice. Dizocilpine-induced hyperactivity (0.1 mg/kg *ip*) in mice was antagonized by all adenosine receptor agonists: CPA – A<sub>1</sub> receptor agonist, CGS 21680 – A<sub>2</sub> receptor agonist, and NECA – A<sub>1</sub>/A<sub>2</sub> agonist, but the effect of NECA was the most apparent. Locomotion induced by the threshold dose of dizocilpine (0.05 mg/kg *ip*) was enhanced by DMPX (A<sub>2A</sub> adenosine receptor antagonist) and by theophylline (A<sub>1</sub> and A<sub>2</sub> receptor antagonist), but not by A<sub>1</sub> receptor antagonist – CPT. These data suggest that adenosinergic system is involved in the mechanism of dizocilpine-induced hyperactivity, and it seems that A<sub>2A</sub> adenosine receptor plays a more important role.

### Key words:

adenosine, dizocilpine, locomotor activity, mice

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### Introduction

Adenosine is known to be a neuromodulator that plays an important role in basal ganglia [9]. Its actions are mediated *via* specific adenosine receptors which are classified into A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> subtypes [14]. Striatopallidal neurons express the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor, dopamine D<sub>2</sub> receptors and adenosine A<sub>2A</sub> receptors [7, 9]. It has also been shown that adenosine modulates excitatory amino acid-mediated neurotransmission by depressing both the release and the postsynaptic action of glutamate [4, 8, 13]. NMDA receptor agonists have been shown to regulate adenosine action in the brain: the administration of NMDA induces biphasic effect on motor activity of mice, with initial motor depression followed by motor activation [10,

15] and evidences suggest that NMDA-induced motor depressive effects are adenosine-mediated because a non-selective adenosine receptor antagonist – theophylline is able to counteract these effects of NMDA [15]. Moreover, stimulation of central NMDA receptors has been shown to increase the extracellular concentrations of adenosine in the brain, including the striatum [3, 19, 31, 32], and NMDA receptor antagonist – dizocilpine completely counteracted this effect [26].

It was also shown that adenosine receptors agonists inhibited electroencephalographic effects induced by dizocilpine [33], neuropathological changes in rat cortex [28] and they blocked the disruptive effects of phencyclidine on prepulse inhibition of the acoustic startle response in rat [35]. Gotoh et al. [16] observed that CPA blocked phencyclidine-induced hyperactivity. Previously, our experiments have shown that locomotor hyperactivity induced by ketamine (another

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NMDA receptor antagonist) was significantly attenuated by adenosine receptor agonist [25].

Dizocilpine (MK-801) is a highly potent and selective, noncompetitive NMDA receptor antagonist [38]. Low doses of dizocilpine induce locomotor stimulation in rats, and typical and atypical neuroleptics antagonize this action [1, 20, 29, 30, 37].

Andine et al. [1] described that dizocilpine-induced hyperactivity in rats was inhibited not only by neuroleptics but also by adenosine receptor agonists, and these authors suggested that dizocilpine-induced behavior represented a rat excitatory amino acid hypofunction model of psychosis that appears to be of clinical relevance, and may be of value in the search for new antipsychotic agents [1].

In the present experiments, we tried to characterize dizocilpine-induced motor activity in mice and to evaluate the influence of adenosine receptor agonists and antagonists on this behavior.

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## Materials and Methods

### Animals

The experiments were carried out on male Albino Swiss mice (18–26 g). The animals were kept 8–10 to a cage under standard laboratory conditions (at a temperature of  $20 \pm 1^\circ\text{C}$  and a 12 h light/dark cycle) with free access to food and water. All experiments were performed between 9:00 a.m. and 4:00 p.m. The experiments were performed in accordance with the opinion of Local Ethics Committee for Animal Experimentation.

### Drugs

The following drugs were used: dizocilpine (MK-801 hydrogen maleate) was purchased from Research Biochemicals International USA, RBI). Adenosine receptor agonists:  $\text{N}^6$ -cyclopentyladenosine (CPA) –  $\text{A}_1$  receptor agonist (RBI, USA), 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS 21680) –  $\text{A}_{2A}$  receptor agonist (RBI, USA), 5'-N-ethylcarboxamidoadenosine (NECA) –  $\text{A}_2/\text{A}_1$  adenosine receptor agonist (RBI, USA). Adenosine receptor antagonists: 8-cyclopentyltheophylline (CPT) –  $\text{A}_1$  receptor antagonist (RBI, USA), 3,7-dimethyl-1-propar-

gylxanthine (DMPX) –  $\text{A}_2$  receptor antagonist (RBI, USA), theophylline – a non-selective adenosine receptor antagonist (Polfa, Poland). All drugs were dissolved in 0.9% saline solution and administered as a single injection intraperitoneally. Control groups received an equivalent volume of 0.9% saline solution.

### Apparatus and procedure

Locomotor activity was measured in a circular activity cages (32 cm in diameter, equipped with two photocell sensor units). Each mouse was placed individually in the cage for 30 min to test its activity, 20 min after injection of dizocilpine (MK-801) and 10 min after injections of adenosine ligands.

### Statistics

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

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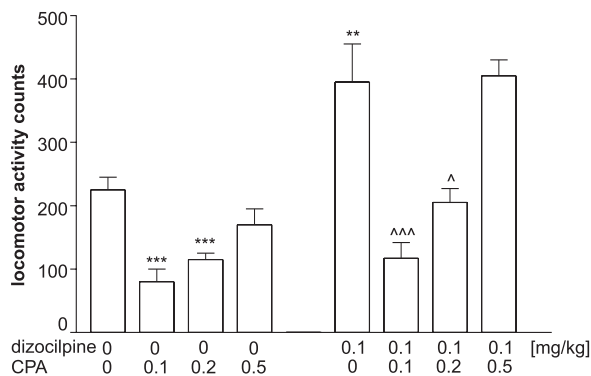
## Results

### The influence of adenosine receptor agonists on the effects of dizocilpine in the locomotor activity test in mice

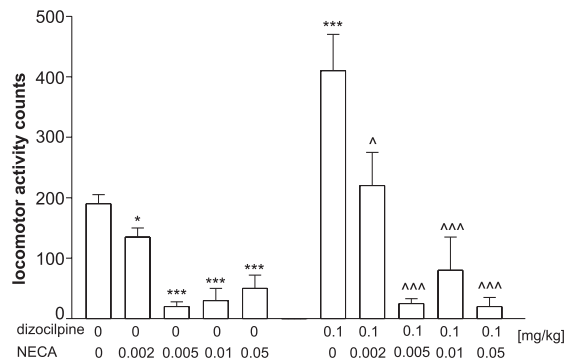
Dizocilpine was injected at doses of 0.1 and 0.05 mg/kg. Higher dose of dizocilpine (0.1 mg/kg) produced marked hyperactivity in mice and this dose was used in the experiments with the agonists of adenosine receptors.

CPA (selective  $\text{A}_1$  adenosine receptor agonist) administered at the doses of 0.1 and 0.2 mg/kg, NECA (nonselective adenosine receptor agonist) at the doses of 0.002–0.05 mg/kg and CGS 21680 (selective  $\text{A}_2$  adenosine receptor agonist) at the doses of 0.05–0.2 mg/kg decreased the locomotor activity in mice, when injected alone (Fig. 1, 2, 3). The highest dose of CPA (0.5 mg/kg) was ineffective in this test (Fig. 1).

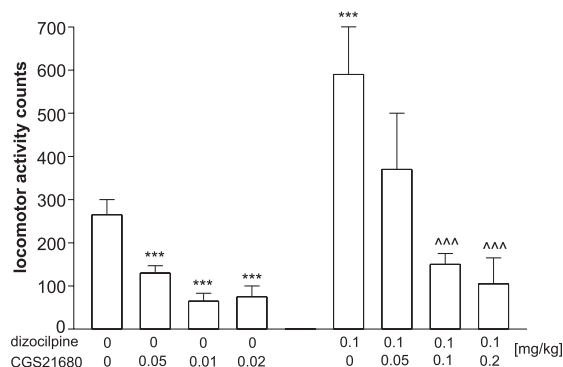
Dizocilpine-induced hyperactivity was depressed by all adenosine receptor agonists, (CPA, CGS 21680, and NECA) but these actions were not greater than those induced by adenosine receptor agonists given alone. (Fig. 1, 2, 3). The action of NECA was the most effective at all doses used (Fig. 3), CGS 21680



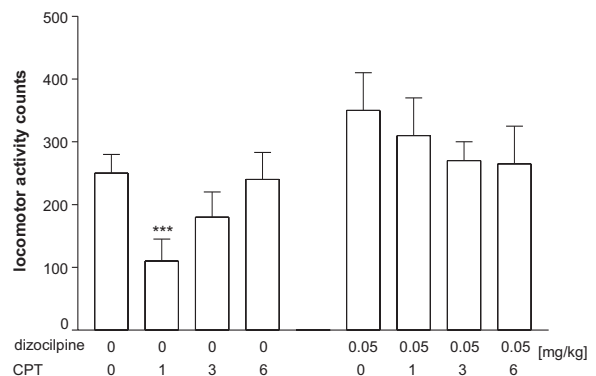
**Fig. 1.** The influence of CPA on dizocilpine-induced hyperactivity in mice. Data represent the mean ( $\pm$  SEM) locomotor activity (counts per 30 min) of 10 mice per group. Mice were pretreated with dizocilpine (0.1 mg/kg) 10 min prior to CPA (0.1, 0.2, 0.5 mg/kg); CPA was administered 10 min before the test. \*\*\*  $p < 0.001$ , \*\*  $p < 0.01$  vs. control vehicle-treated group, ^^^  $p < 0.001$ , ^  $p < 0.05$  vs. dizocilpine-treated group (Student's *t*-test).



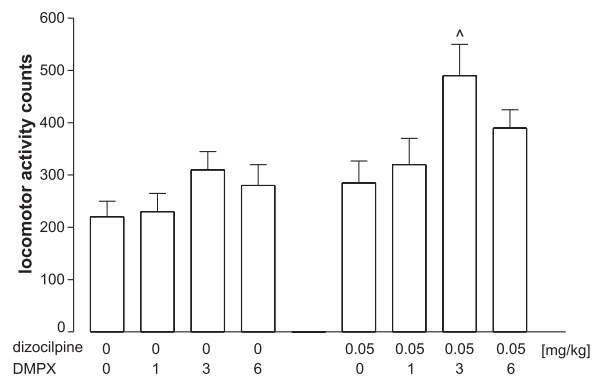
**Fig. 2.** The influence of NECA on dizocilpine-induced hyperactivity in mice. Data represent the mean ( $\pm$  SEM) locomotor activity (counts per 30 min) of 10 mice per group. Mice were pretreated with dizocilpine (0.1 mg/kg) 10 min prior to NECA (0.002, 0.005, 0.01, 0.05 mg/kg); NECA was administered 10 min before the test. \*\*\*  $p < 0.001$ , \*  $p < 0.05$  vs. control vehicle-treated group, ^^^  $p < 0.001$ , ^  $p < 0.05$  vs. dizocilpine-treated group (Student's *t*-test).



**Fig. 3.** The influence of CGS 21680 on dizocilpine-induced hyperactivity in mice. Data represent the mean ( $\pm$  SEM) locomotor activity (counts per 30 min) of 10 mice per group. Mice were pretreated with dizocilpine (0.1 mg/kg) 10 min prior to CGS 21680 (0.05, 0.1, 0.2 mg/kg); CGS 21680 was administered 10 min before the test. \*\*\*  $p < 0.001$  vs. control vehicle-treated group, ^^^  $p < 0.001$  vs. dizocilpine-treated group (Student's *t*-test).



**Fig. 4.** The influence of CPT on dizocilpine-induced locomotor activity in mice. Data represent the mean ( $\pm$  SEM) locomotor activity (counts per 30 min) of 10 mice per group. Mice were pretreated with dizocilpine (0.05 mg/kg) 10 min prior to CPA (1, 3, 6 mg/kg); CPT was administered 10 min before the test. \*\*\*  $p < 0.001$ , \*\*  $p < 0.01$  vs. control-treated group (Student's *t*-test).

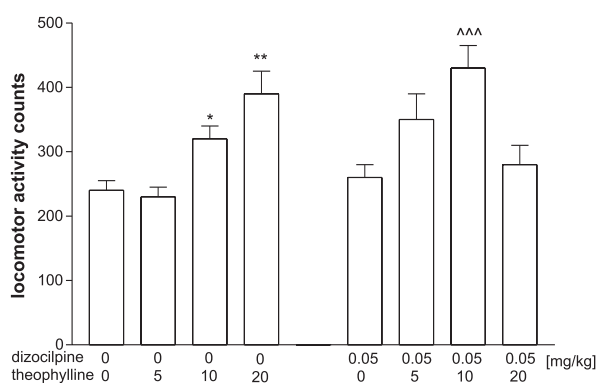


**Fig. 5.** The influence of DMPX on dizocilpine-induced locomotor activity in mice. Data represent the mean ( $\pm$  SEM) locomotor activity (counts per 30 min) of 10 mice per group. Mice were pretreated with dizocilpine (0.05 mg/kg) 10 min prior to DMPX (1, 3, 6 mg/kg); DMPX was administered 10 min before the test. ^  $p < 0.05$  vs. dizocilpine-treated group (Student's *t*-test).

evoked similar effect at the higher doses of 0.1 and 0.2 mg/kg (Fig. 2), but CPA antagonized the effect of dizocilpine only at the two lower doses of 0.1 and 0.2 mg/kg. The highest dose of CPA (0.5 mg/kg) was ineffective (Fig. 1).

### The influence of adenosine receptor antagonists on the effects of dizocilpine in the locomotor activity test in mice

Lower dose of dizocilpine (0.05 mg/kg) did not influence the locomotor activity in mice, and this dose was used in experiments with adenosine receptor antagonists (Fig. 4, 5, 6).



**Fig. 6.** The influence of theophylline on dizocilpine-induced locomotor activity in mice. Data represent the mean ( $\pm$  SEM) locomotor activity (counts per 30 min) of 10 mice per group. Mice were pretreated with dizocilpine (0.05 mg/kg) 10 min prior to theophylline (5, 10, 20 mg/kg); theophylline was administered 10 min before the test. \*\*  $p < 0.01$ , \*  $p < 0.05$  vs. control vehicle-treated group, ^^^  $p < 0.001$  vs. dizocilpine-treated group (Student's  $t$ -test)

Selective blockade of adenosine  $A_1$  receptors by CPT administered at the dose of 1 mg/kg decreased locomotor activity in mice but higher doses of CPT (3 and 6 mg/kg) did not change motility of mice. All administered doses of CPT did not influence the effects of dizocilpine in this test (Fig. 4). Selective blockade of adenosine  $A_2$  receptors by DMPX (1–6 mg/kg) did not produce any action (when given alone), but DMPX enhanced the effects of dizocilpine only at the dose of 3 mg/kg (Fig. 5). Theophylline, a non-selective adenosine receptor antagonist, given alone, did not produce any action at the dose of 5 mg/kg, but the higher doses (10 and 20 mg/kg) induced an increase in motor activity of mice, and the dose of 10 mg/kg was able to enhance the effects of dizocilpine in this test (Fig. 6).

## Discussion

In the present experiments, dizocilpine when injected at the dose of 0.1 mg/kg *ip*, induced hyperactivity in mice, but at the lower dose of 0.05 mg/kg *ip*, had almost no influence on locomotion. These observations are consistent with other reports concerning dizocilpine-induced locomotor effects in mice [2, 6, 23].

It is well known that dopaminergic mechanisms play an important role in locomotor behavior [12]. Dizocilpine-induced hyperlocomotion is partly medi-

ated by NMDA receptor antagonism [22], and may also involve dopaminergic mechanisms, since it is inhibited by  $D_2$  receptor antagonists – neuroleptics [1, 20, 22, 29, 30, 37]. It was shown that dizocilpine was able to enhance the release of dopamine from isolated striatal nerve endings [36], thus, NMDA receptor antagonism may result in an increased dopamine release [21].

Our studies demonstrate that dizocilpine-induced hyperactivity in mice is also influenced by adenosine receptor mechanisms: it is antagonized by all adenosine receptor agonists used in the present experiments, and NECA ( $A_2/A_1$  receptor agonist) has the most apparent action. Selective  $A_1$  (CPA) and  $A_{2A}$  (CGS 21680) receptor agonists antagonize this effect of dizocilpine at doses (0.1 and 0.2 mg/kg). CPA administered at dose of 0.5 mg/kg has no influence on control mice, and on those treated with dizocilpine, so, dizocilpine hyperactivity is reduced only by effective doses (0.1 and 0.2 mg/kg) of CPA. However,  $A_{2A}$  receptor agonist – CGS 21680 reduces dizocilpine effects dose-dependently. Active doses of CPA and CGS 21680 are 50–100 times higher than minimal effective dose of NECA (0.002 mg/kg). Thus simultaneous activation of both adenosine receptors produced the strongest effects. This our result is in agreement with the observations of Andine et al. [1] in rats, although these authors used higher doses of NECA and CGS 21680. Thus, adenosine  $A_1$  and  $A_{2A}$  receptor agonists are able to block dizocilpine-induced hyperactivity in mice (our results) and rats [1], and their actions are similar to those of neuroleptics (see above).

In our experiments with adenosine receptors antagonists, locomotion induced by the threshold dose of dizocilpine (0.05 mg/kg *ip*) was enhanced by DMPX ( $A_{2A}$  adenosine receptor antagonist) and by theophylline ( $A_1$  and  $A_2$  receptor antagonist), but  $A_1$  receptor antagonist (CPT) was without effect. This means that behavioral activation observed with the threshold dose of dizocilpine and adenosine receptor antagonist seems to be  $A_{2A}$  receptor mediated, and this observation confirms suggestions of other authors that  $A_{2A}$  adenosine receptor plays the main role in locomotion [17, 27]. Similar results were observed in our previous paper concerning ketamine-induced hyperactivity in which DMPX and caffeine, but not DPCPX (another  $A_1$  receptor antagonist) increased ketamine-induced activity in mice [25].  $A_{2A}$  receptors are expressed and co-localized with  $D_2$  receptors in striatopallidal neurons [11, 34], and the data indicate that adenosine plays an opposite role to dopamine in

the brain [9]. Behavioral effects of adenosine  $A_{2A}$  receptor agonists are similar to those induced by neuroleptics –  $D_2$  receptor antagonists, and antagonists of  $A_{2A}$  adenosine receptors can reverse various dopamine related motor impairments, such as locomotor suppression, catalepsy or rigidity [5, 18, 24]. Such interactions between the brain dopamine and adenosine receptors may explain the inhibitory action of adenosine receptor agonists and facilitating effects of adenosine receptor antagonists on dizocilpine hyperlocomotion observed in our experiments.

In conclusion, the present results have shown that adenosinergic system is involved in the mechanism of dizocilpine action since agonists of  $A_1$  and  $A_{2A}$  receptors are able to antagonize MK-801 induced hyperactivity, and simultaneous activation of both adenosine receptors (NECA) produced the most apparent effect. Adenosine receptor antagonists (particularly  $A_{2A}$ ) are able to enhance dizocilpine-induced hyperactivity in mice. Thus, the actions of adenosine receptor agonists are similar to those of neuroleptics [20, 22, 29, 30, 37]. Our present observations in mice confirm the findings of Andine et al. [1] in rats, and corroborate the suggestions of these authors that dizocilpine-induced behavior may be of value in the search for new antipsychotic agents.

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