Polish Journal of Pharmacology
Pol. J. Pharmacol., 2003, 55, 319–326
ISSN 1230-6002

EFFECTS OF ADENOSINE RECEPTOR AGONISTS AND ANTAGONISTS IN AMPHETAMINE-INDUCED CONDITIONED PLACE PREFERENCE TEST IN RATS

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Effects of adenosine receptor agonists and antagonists in amphetamine-induced conditioned place preference test in rats. E. POLESZAK, D. MALEC. Pol. J. Pharmacol., 2003, 55, 319–326.

The influence of adenosine receptor agonists and antagonists on amphetamine-induced conditioned place preference (CPP) was examined in male Wistar rats. Selective adenosine A1 receptor agonist, CPA, significantly reduced the acquisition of CPP induced by amphetamine. NECA (A2/A1 adenosine receptor agonist) produced similar effect, but selective A2 adenosine receptor agonist CGS 21680, attenuated acquisition of amphetamine-induced CPP only at the lower dose used. The blockade of adenosine receptors by CPT, DMPX and caffeine, did not influence the expression and acquisition of amphetamine-induced CPP. With regard to the expression of amphetamine-induced CPP, only A2A adenosine agonist (CGS 21680) slightly decreased the action of amphetamine. Other adenosine agonists were without effect. Our results indicate that activation of A1 receptor decreases the acquisition of CPP induced by amphetamine. It suggests that adenosine A1 receptor is involved in rewarding effects of amphetamine. Therefore, it seems that selective adenosine A1 receptor agonists may have some attenuating influence on the development of amphetamine dependence.

Key words: *amphetamine, adenosine, CPP-test, rats*

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INTRODUCTION

The purine nucleoside, adenosine, and its various receptor subtypes play multiple functions in the modulation of different central nervous system activities [10, 12, 15, 17, 26, 30].

Four adenosine receptors (A1, A2A, A2B, A3), belonging to the family of G protein-coupled receptors, have been cloned and pharmacologically characterized so far [16]. In the brain, adenosine receptors are abdundantly expressed in neurons and certain glial cells. A1 receptors are widely distributed in the brain, particularly in the hippocampus, cerebellum, neocortical areas [11, 16], and the high density of A1 receptors is present in the striatum [1, 16]. Stimulation of presynaptic A1 receptors suppresses the neuronal firing and inhibits transmitter release [15]. A2A adenosine receptors are highly concentrated in the striatum, particularly, in the GABAergic striopallidal neurons where they are colocalized with dopamine D2 receptors [14, 21] and they can influence each other functionally. In particular, a strong antagonistic interaction between adenosine A2A and dopamine D2 receptors seems to take place in the striopallidal GABAergic neurons which originate in the ventral striatum [12]. Stimulation of the A2A receptor leads to a reduction in the affinity of D2 receptors for D2 receptor agonists [12]. The anatomical studies have shown that these interactions can take place in the striatum, where A2A and D2 and A1 and D1 receptors are colocalized [13]. Some behavioral effects induced by adenosine receptor agonists or antagonists also suggest the existence of an antagonistic A1-D1 interaction [13].

Very few studies have investigated the involvement of A2A adenosine neurotransmission in motivation/reward processes. In more recent studies, selective A2A receptor agonists (CGS 21680 or APEC) were found to attenuate the rewarding impact of brain stimulation, whereas selective antagonists of adenosine A2 receptors (CSC or DMPX) did not alter reward threshold [2, 3].

Our previous study demonstrated that adenosine receptor antagonists (DMPX, CPT, caffeine) markedly and significantly decreased the expression of CPP induced by cocaine [28]. On the basis of the above findings, we decided to evaluate in the present studies the influence of adenosine receptor ligands on the rewarding properties induced by another dopaminergic stimulant, amphetamine, in the CPP test. Such experiments have not been performed so far. Amphetamine is able to stimulate dopaminergic neurons mainly by increasing dopamine release [22, 33] from nerve terminals, and this action is responsible for many of the behavioral effects, such as rewarding and locomotor stimulant properties [23].

MATERIALS and METHODS

Amphetamine-induced CPP was examined in male Wistar rats, weighing 200–250 g (6 in a group). The animals were kept in controlled conditions (under 12/12h light/dark cycle, at ambient temperature of 20 ± 1°C) with free access to food and water. The studies were performed between 8.00–16.00.

Apparatus

Apparatus consisted of 4 rectangular wooden boxes (60 × 35 × 30 cm). Each of them was divided into 3 compartments (25 × 35 cm) that were separated by the guillotine doors with a grey area in the center (10 × 10 cm). The walls of the large compartments differed in color, one having black walls, the other having white walls. The boxes were kept in a sound-proof room with constant light provided by a 40 W bulb.

Procedure (performed according to Carr et al. [7])

There were 3 phases of behavioral test protocols: pre-conditioning, conditioning and post-conditioning. During the pre-conditioning phase (one-day), the baseline preference of rats was determined. Each rat was placed in the central grey area and allowed to explore 3 compartments of the boxes for 15 min. The time spent by each animal in non-preferred compartment was recorded.

The white compartment was paired with amphetamine during the conditioning phase, lasting 3 days.

To measure the effects of adenosine receptor ligands on the acquisition of amphetamine-induced CPP, the rats were injected with saline *ip* and were confined for 30 min to the initially preferred (black) compartment. After 4 h, the animals were pretreated with adenosine ligands, and 10 min later they received injection of amphetamine (1 mg/kg), before being placed in the initially non-preferred (white) compartment for 30 min. To determine the effects of adenosine ligands, appropriate group of rats was injected with adenosine ligands alone and placed in the white compartment, similarly as amphetamine-injected groups.

During the post-conditioning phase (next day), the guillotine doors that separated compartments were removed, and the time spent by each rat in the non-preferred compartment was recorded during the trial lasting 15 min.

A similar procedure was applied to measure the effects of adenosine ligands on the expression of amphetamine-induced CPP: rats were treated with amphetamine during 3 days of the conditioning trials, and were injected with adenosine ligands given acutely, 20 min before the post-conditioning. Appropriate group of animals received saline during conditioning, and a single injection of adenosine ligands on the post-conditioning day.

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 non-selective adenosine receptor antagonist (Polfa, Poland), 8-cyclopentyltheophylline (CPT), A1 receptor antagonist (RBI, USA), 3,7-dimethyl-1-propargylxanthine (DMPX), A2 receptor antagonist (RBI, USA),

— drug stimulating dopaminegic neurotransmission: D-amphetamine sulfate (Sigma, USA).

All drugs were dissolved in saline and doses were injected according to those used in our previous study [28]. Control animals received the same volume of saline.

Data analysis

Data were expressed as time (mean ± SEM; in seconds) spent in the non-preferred compartment after conditioning. Statistical analysis was carried out by the one-way analysis of variance (ANOVA), followed by the Bonferroni test. The probability level of $p < 0.05$ was considered as statistically significant.

RESULTS

On the pre-conditioning day, the rats spent significantly more time in the black compartment than in the white compartment. These site preferences were not significantly different between the groups. The natural preferences of rats were not changed by saline injections during the conditioning sessions.

Effect of CGS 21680 on the acquisition and expression of CPP induced by amphetamine

In the acquisition test the data were expressed as a time (in seconds) spent in the drug-associated (white) compartment. One-way ANOVA showed a significant difference between drug treatment groups [$F(5,34) = 7.67$, $p < 0.0001$]. Post-hoc analysis revealed that amphetamine administration (at the dose of 1 mg/kg *ip*) during conditioning days induced a significant place preference ($p < 0.01$) in the testing phase of the experiment, in comparison with animals that received saline injection during all conditioning days (control group) (Fig. 1A). CGS 21680, given alone, induced place preference at the dose of 0.25 mg/kg ($p < 0.05$) (Fig. 1) and administered with each injection of amphetamine during the conditioning sessions prevented acquisition of amphetamine-induced CPP only at the lower dose used, i.e. 0.25 mg/kg ($p < 0.001$) (Fig. 1A).

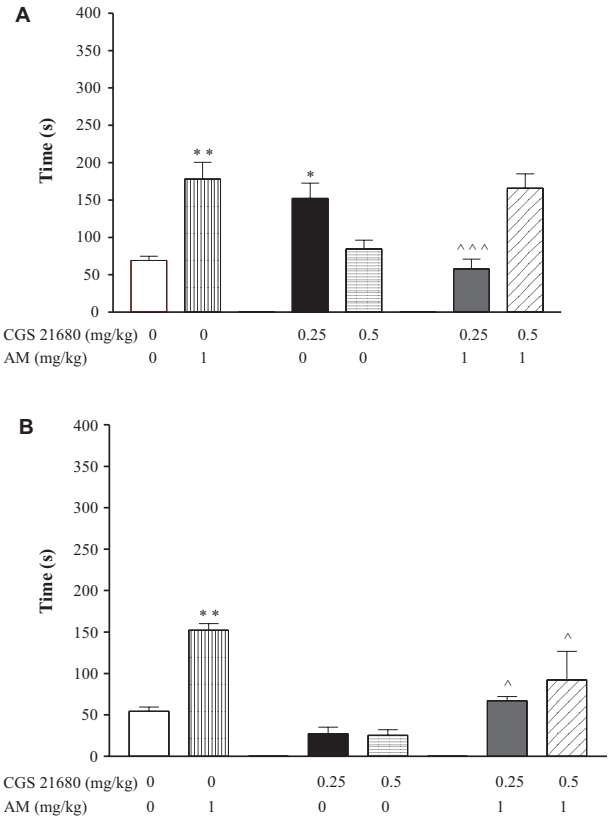

Fig. 1. The influence of CGS 21680 on acquisition (A) and expression (B) of CPP induced by amphetamine (AM). Explanations: 0 – 0.9% NaCl, * $p < 0.05$ – vs. 0.9% NaCl, ** $p < 0.01$ – vs. 0.9% NaCl, ^ $p < 0.05$ – vs. amphetamine + 0.9% NaCl, ^ ^ ^ $p < 0.001$ – vs. amphetamine + 0.9% NaCl

In the expression test, one-way ANOVA indicated significant differences between the groups [F(5,34) = 9.107, p < 0.0001]. Post-hoc analysis showed that amphetamine-treated rats during conditioning induced a significant preference for the drug-associated compartment (p < 0.01) (Fig. 1B). CGS 21680, given acutely to saline-treated groups on the test day, did not change the time spent by rats in drug-associated compartment (Fig. 1B). CGS 21680 (0.25 and 0.5 mg/kg), given as a single injection before the post-test phase to the rats previously conditioned with amphetamine, prevented the expression of amphetamine-induced CPP slightly and not dose-dependently (p < 0.05) (Fig. 1B).

Effect of NECA on the acquisition and expression of CPP induced by amphetamine

In the acquisition test, one-way ANOVA indicated significant differences between the groups [F(5,34) = 5.45, p = 0.0009]. Post-hoc analysis showed that amphetamine-treated rats during conditioning induced a significant preference for the drug-associated compartment (p < 0.001) (Fig. 2A). NECA, given alone, induced place preference when administered at doses of 0.005 mg/kg (p < 0.001) and 0.02 mg/kg (p < 0.01) (Fig. 2A) and at these doses significantly decreased the acquisition of amphetamine CPP (p < 0.01) (Fig. 2A).

In the CPP expression test, one-way ANOVA also indicated differences between the groups [F(5,26) = 3.47, p = 0.015]. Post-hoc analysis showed that NECA, given acutely to saline groups on the test day, did not change the time spent by rats in the drug-associated compartment in comparison with control animals (Fig. 2B) and did not influence the expression of place preference produced by amphetamine (Fig. 2B).

Effect of CPA on the acquisition and expression of CPP induced by amphetamine

In the acquisition test, one-way ANOVA indicated significant differences between the groups [F(5,34) = 11.77, p < 0.0001]. Post-hoc analysis showed that amphetamine-treated rats during conditioning induced a significant preference for the drug-associated compartment (p < 0.001). CPA (0.05 and 0.1 mg/kg) given alone induced place preference at the both administered doses (p < 0.05) and significantly decreased the acquisition of amphetamine-induced CPP (p < 0.001) (Fig. 3A).

In the expression test, one-way ANOVA indicated significant differences between the groups [F(5,26) = 2.28, p = 0.075]. Post-hoc analysis showed that CPA, given acutely to saline groups on the test day, induced a significant decrease of the time spent by rats in drug-associated compartment (Fig. 3B) and did not change the expression of amphetamine-induced CPP (Fig. 3B).

Effect of DMPX on the acquisition and expression of CPP induced by amphetamine

In the both tests (acquisition and expression) one-way ANOVA showed differences between drug treatment groups, respectively [F(5,34) = 3.95 p = 0.006 and F(5,35) = 6.27 p = 0.0003]. Post-hoc analysis showed that DMPX (selective A2 adenosine receptor antagonist) influenced neither expression nor acquisition of the amphetamine-induced CPP (Fig. 4A, 4B).

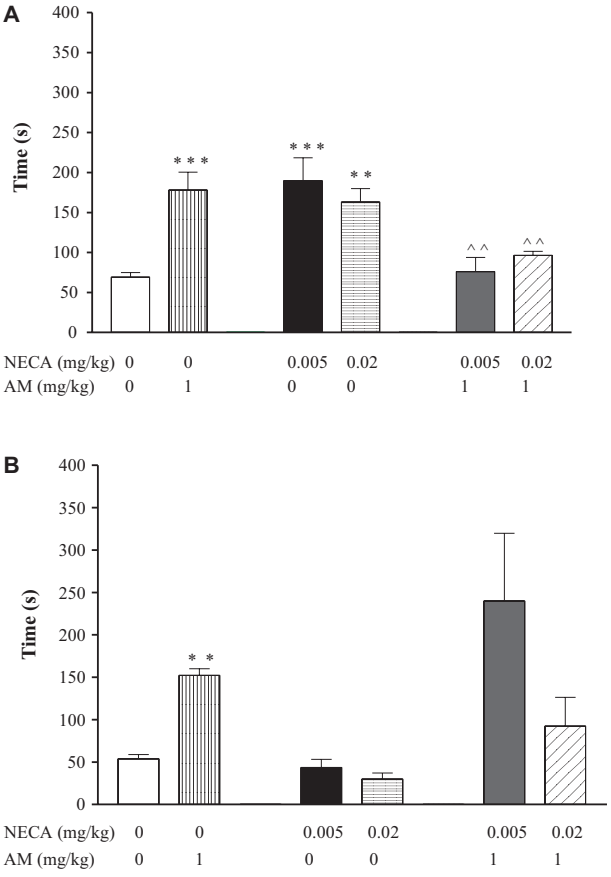

Fig. 2. The influence of NECA on acquisition (A) and expression (B) of CPP induced by amphetamine (AM). Explanations: 0–0.9% NaCl, ** p < 0.01 – vs. 0.9% NaCl, *** p < 0.001 – vs. 0.9% NaCl, ^ ^ p < 0.01 – vs. amphetamine + 0.9% NaCl

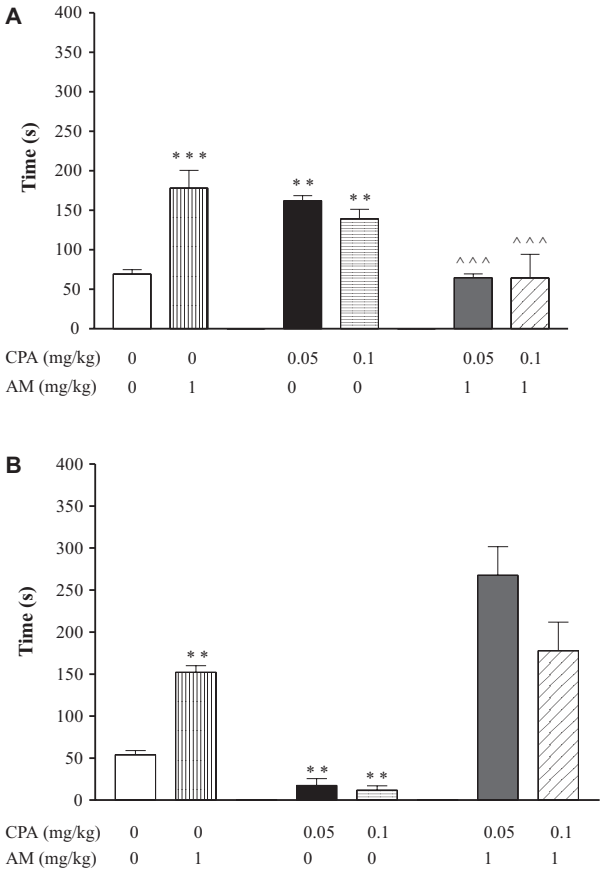

Fig. 3. The influence of CPA on acquisition (A) and expression (B) of CPP induced by amphetamine (AM). Explanations: 0 – 0.9% NaCl, ** $p < 0.01$ – vs. 0.9% NaCl, *** $p < 0.001$ – vs. 0.9% NaCl, ^ ^ ^ $p < 0.001$ – vs. amphetamine + 0.9% NaCl

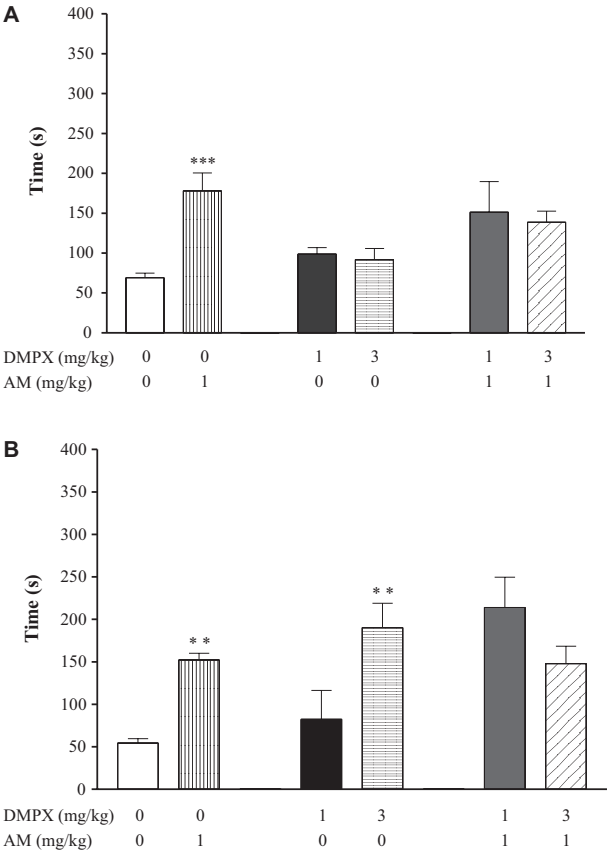

Fig. 4. The influence of DMPX on acquisition (A) and expression (B) of CPP induced by amphetamine (AM). Explanations: 0 – 0.9% NaCl, *** $p < 0.001$ – vs. 0.9% NaCl, ** $p < 0.01$ – vs. 0.9% NaCl

Effect of CPT on the acquisition and expression of CPP induced by amphetamine

In the acquisition test one-way ANOVA showed differences between the groups [$F(5,34) = 5.05$ $p = 0.0014$]. The post-hoc test showed that CPT administered with amphetamine during the conditioning sessions decreased the action of amphetamine only at the lower dose of 1.0 mg/kg ($p < 0.05$) (Fig. 5A). CPT, given alone, did not change the time spent by rats in the drug-associated compartment in comparison with control animals (Fig. 5A).

In the expression test, one-way ANOVA indicated differences between the groups [$F(5,24) = 8.89$ $p < 0.0001$] The post-hoc test analysis showed that CPT, given as a single injection before the post-test phase to the rats previously conditioned with amphetamine (expression test), did not influence the amphetamine action (Fig. 5B).

Effect of caffeine on the acquisition and expression of CPP induced by amphetamine

In the acquisition test, one-way ANOVA showed differences between the groups [$F(5,35) = 2.62$ $p = 0.04$]. The post-hoc test analysis indicated that caffeine did not change the time spent in the white compartment in comparison with control animals. At the higher dose of 20 mg/kg slightly attenuated the acquisition of amphetamine-induced CPP ($p < 0.05$) (Fig. 6A).

In the expression test one-way ANOVA showed significant differences between the groups [$F(5,27) = 9.52$ $p < 0.0001$]. Caffeine given only at the lower dose used (10 mg/kg), slightly enhanced the expression of amphetamine-induced CPP ($p < 0.05$). However, caffeine at the doses of 10 mg/kg ($p < 0.01$) and 20 mg/kg ($p < 0.001$), given alone to saline groups on the test day, induced a significant in-

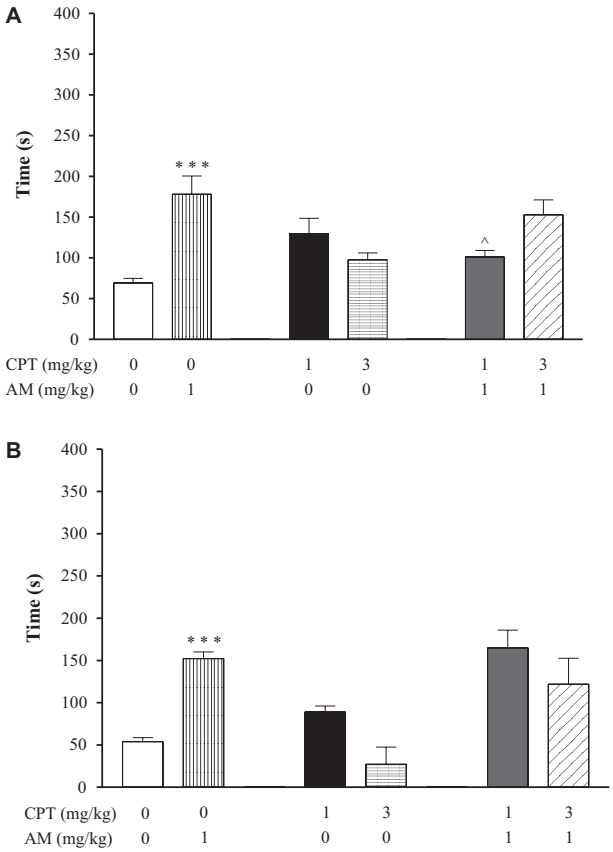

Fig. 5. The influence of CPT on acquisition (A) and expression (B) of CPP induced by amphetamine (AM). Explanations: 0–0.9% NaCl, *** $p < 0.001$ – vs. 0.9% NaCl, ^ $p < 0.05$ vs. amphetamine + 0.9% NaCl

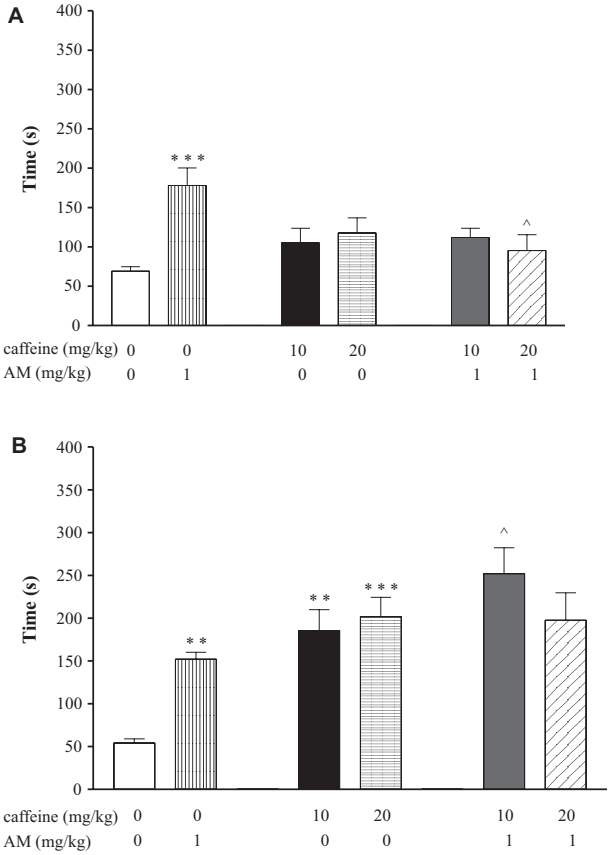

Fig. 6. The influence of caffeine on acquisition (A) and expression (B) of CPP induced by amphetamine (AM). Explanations: 0–0.9% NaCl, *** $p < 0.001$ – vs. 0.9% NaCl, ** $p < 0.01$ – vs. 0.9% NaCl, ^ $p < 0.05$ – vs. amphetamine + 0.9% NaCl

crease of the time spent by rats in drug-associated compartment (Fig. 6B).

DISCUSSION

Conditioned place preference (CPP) is a behavioral test for measuring the motivational/rewarding processes in animals [7]. Amphetamine is known to induce a positive CPP [8, 9].

In our experiments, all adenosine receptors agonists, when given alone, produced also some positive actions in the acquisition of CPP, but the effects were not dose-dependent. Other authors observed that agonists and antagonists of adenosine receptors, given alone, were able to evoke various responses in CPP test. For example, Brockwell and Beninger [5] and Brockwell et al. [6] have observed in rat that agonists of adenosine receptors (CPA and CGS 21680) failed to produce significant place conditioning, but Zarrindast and Moghadamnia [36] have shown that A1 adenosine receptor agonists (R-PIA, CHA) induced conditioned place aversion in mice, whereas NECA evoked CPP. As we mentioned above (Introduction), Baldo and Koob [2] and Baldo et al. [3] described that selective A2A agonists were found to attenuate the rewarding impact of brain stimulation, whereas selective A2 receptor antagonists did not alter reward threshold. Thus, the effects of adenosine analogs are different and not clear. In general, drugs blocking DA neurotransmission (like neuroleptics) do not induce positive responses in CPP and abolish the effects of drugs of abuse [18], although some atypical neuroleptics have been shown to increase the food-induced CPP in rats and these effects were related to the enhancement of dopaminergic neurotransmission as the result of the blockade of presynaptic DA D2 receptors [18]. Maybe the effects observed in our experiments with adenosine agonists in acquisition of CPP are similar to those of atypical neuroleptics,

and indicate that adenosinergic neurotransmission may be involved in rewarding mechanisms.

All adenosine analogs influenced the response of rats in amphetamine-induced CPP in the present studies: selective adenosine A1 receptor agonist CPA significantly reduced the acquisition of CPP induced by amphetamine. NECA (A2/A1 adenosine receptor agonist) produced similar effect, but selective A2 adenosine receptor agonist CGS 21680 attenuated acquisition of amphetamine-induced CPP only at the lower dose used. Thus, the most effective influence on amphetamine action in the CPP test was observed after A1 receptor stimulation. This reducing effect of adenosine A1 agonist (CPA) may probably be related to the inhibition of dopamine release by presynaptic A1 adenosine receptor stimulation [15], an effect which is opposed to the main mechanism of amphetamine action [22, 33]. Therefore, our results confirm the existence of an antagonistic A1 – D1 receptor interaction [13] and indicate that adenosine A1 receptor is also involved in rewarding effects of amphetamine in the acquisition phase of CPP test.

The blockade of adenosine receptors by CPT, DMPX and caffeine had nearly no influence on the expression and acquisition of amphetamine-induced CPP. These results with adenosine receptors antagonists are in contrast with our previous experiments in which CPT, DMPX and caffeine markedly and significantly decreased the expression of cocaine-induced CPP. Both cocaine and amphetamine potentiate dopaminergic neurotransmission, however, their mechanisms are different: they both block dopamine uptake through binding to the dopamine transporter [22, 24, 27, 31] but only amphetamine affects dopamine release [22, 33].

In the expression phase of amphetamine-induced CPP, only A2A adenosine receptor agonist (CGS 21680) slightly decreased the action of amphetamine (the effect was statistically significant, but not dose-dependent). Other adenosinergic agonists were without any effect. Thus, it seems that adenosine receptors are less involved in the expression of CPP induced by amphetamine, although A2A adenosine receptor stimulation may have some influence. In the CPP expression test, all adenosinergic ligands were injected only once, but in the acquisition test they were administered for 3 days. It may be that longer stimulation of adenosine receptors (acquisition test) induces more apparent interactions between adenosine and dopamine receptors than after acute injection of adenosinergic ligands (expression test).

Dopamine D1 receptors seem to play central roles in mediating both acute and chronic effects of psychostimulants in rodents [35]. Pharmacological studies have shown that D1 receptor agonists and antagonists can influence CPP to an amphetamine paired environment [19]. Liao et al. [25] have shown that dopamine D1 and D2 receptor antagonists (SCH 23390 and spiperone) inhibited amphetamine-induced expression of CPP. Thus, both D1 and D2 dopamine receptors seem to play a role in amphetamine rewarding properties [4].

The mesolimbic dopamine system and, particularly, its terminals in the nucleus accumbens septi (NAS), have been considered to be an important neurobiological substrate for the rewarding and psychomotor activating effects of psychostimulants [23, 29, 34]. For example, intra-accumbens injections of amphetamine induce CPP [8, 9], and lesions of dopaminergic neurons in NAS by 6-hydroxydopamine (6-OHDA) [32] and dopamine receptor antagonists [20, 32] block amphetamine-induced CPP.

In summary, our results suggest that adenosine A1 receptor is involved in rewarding effects of amphetamine in acquisition test, and its activation decreases the acquisition of CPP induced by amphetamine. Therefore, it seems that selective adenosine A1 receptor agonists may have some attenuating influence on the development of amphetamine dependence.

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Received: December 2, 2002; in revised form: March 31, 2003.