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ADENOSINE RECEPTOR LIGANDS AND COCAINE IN CONDITIONED PLACE PREFERENCE (CPP) TEST IN RATS

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The influence of adenosine receptor agonists and antagonists on cocaine-induced conditioned place preference (CPP) was examined in male Wistar rats. Adenosine receptor agonists, when given alone, induced place preference in some dose ranges, and it seems that adenosine A1 and A2 receptors might be involved in this reaction. 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 did not prevent the acquisition of cocaine-induced CPP but, when administered at the lower doses, they reduced the expression of cocaine action in CPP test. Selective adenosine A1 receptor antagonist, 8-cyclopentyltheophylline (CPT), A2 receptor antagonist, 3,7-dimethyl-1-propargylxanthine, DMPX, and caffeine (non-selective A1/A2 receptor antagonist) markedly and significantly decreased the expression of CPP induced by cocaine, and caffeine (20 mg/kg) decreased also the acquisition of this reaction. Our results suggest the involvement of adenosine A1 and A2 receptors in rewarding properties of cocaine measured in CPP test.

Key words: *cocaine, adenosine, CPP test, rats*

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INTRODUCTION

Adenosine is a neuromodulator in the central nervous system and its effects are mediated *via* four distinct receptor subtypes: A1, A2A, A2B, A3 [14]. A1 receptors are widely expressed in the brain, while A2A receptors are restricted to dopamine (DA)-innervated areas, such as the dorsal striatum, nucleus accumbens (ventral striatum) and olfactory tubercle. Adenosine, acting *via* presynaptic A1 receptors, suppresses the neuronal firing and inhibits transmitter release [15]. A2B receptors have ubiquitous distribution in the brain and most probably play a role under pathological conditions, since they are only activated by high adenosine concentrations [14], and A3 receptor seems to be poorly expressed in the brain [14, 38]. There is an evidence for the existence of antagonistic interaction between the neurotransmitter DA and the neuromodulator adenosine in the ventral striatum. In particular, a strong antagonistic interaction between adenosine A2A and 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].

Psychostimulant cocaine inhibits the DA transporter and indirectly activates DA neurotransmission [32]. It is a widely abused drug with powerful reinforcing properties. Dopaminergic stimulation in the mesolimbic system, particulary in the nucleus accumbens, is involved in locomotor hyperactivity, sensitizing, discriminative stimulus effects and rewarding properties of cocaine [3, 6, 7, 10, 18, 35].

Conditioned place preference (CPP) is a behavioral test for measuring the rewarding properties of drugs in animals [8], and cocaine is known to induce positive place preference.

Drugs which block DA neurotransmission (like neuroleptics) do not induce positive reinforcement and even produce conditioned aversion or abolish the effects of drugs of abuse [19]. However, it was shown that some neuroleptics (sulpiride, pimozide, amisulpride) increased 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 [19]. Thus, the blockade of DA D2 receptors may produce both the inhibition of place preference or place aversion, and sometimes it may induce an increase in CPP.

Since dopaminergic D2 receptors are co-localized with adenosine A2A receptors, and they are functionally antagonistic [12, 29], thus, it seems possible that agonists of adenosine A2A receptor may have similar action as neuroleptics in CPP test.

Abovementioned antagonistic interaction between DA and adenosine in the brain prompted us to examine the effects of adenosine receptor agonists and antagonists in the CPP test, and their influence on cocaine-induced place preference in rats.

MATERIALS and METHODS

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). Dopamine receptor agonist: cocaine (Sigma, USA).

All drugs were dissolved in saline. Control animals received the same volumes of saline.

Cocaine CPP was examined in male Wistar rats (6 in the group). The animals were kept in rooms under controlled conditions (under 12/12 h light/dark cycle, at ambient temperature of 20 ± 1°C) with free access to food and water.

Apparatus

Apparatus consisted of 4 rectangular woodden boxes (60 × 35 × 30 cm) each of them 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

There were 3 phases of behavioral 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 cocaine during the conditioning phase, lasting 3 days.

To measure the effects of adenosine ligands on the acquisition of cocaine-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 cocaine (5 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 cocaine-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 cocaine-induced CPP: rats were treated with cocaine during 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.

Data analysis

Data were expressed as time (mean ± SEM; in s) 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 place preferences were not significantly different between the groups. The natural preferences of rats were not changed by saline injections during the conditioning sessions.

Cocaine at the dose of 5 mg/kg *ip* increased the time spent by rats in the non-preferred (white) compartment during the post-test phase, as compared with the control group (Fig. 1–12). CGS 21680 given alone, increased the time spent by rats in the non-preferred compartment only at the lower dose used (Fig. 1). CGS 21680 administered with cocaine during the conditioning sessions did not prevent acquisition of cocaine-induced CPP (Fig. 1). CGS 21680 given as a single injection before the post-test phase to the rats previously conditioned with cocaine, prevented the expression of cocaine-induced CPP only at the lower dose of 0.25 mg/kg (Fig. 2).

NECA given alone increased the time spent by rats in the non-preferred compartment (Fig. 3), but did not influence the cocaine-induced CPP in the test measuring acquisition of CPP (Fig. 3). However, NECA attenuated the expression of place

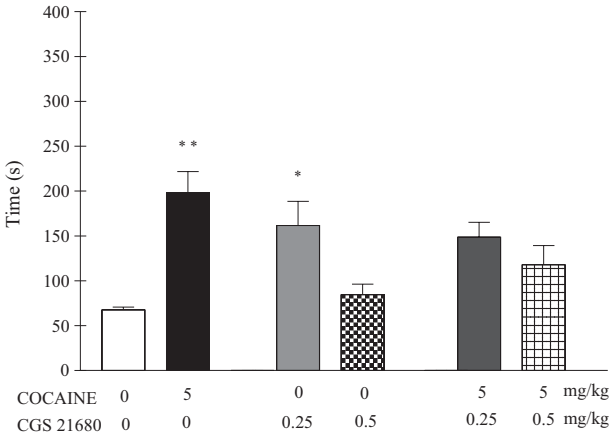

Fig. 1. The influence of CGS 21680 on acquisition of CPP induced by cocaine; ** $p < 0.01$, * $p < 0.05$ – compared to 0.9% NaCl

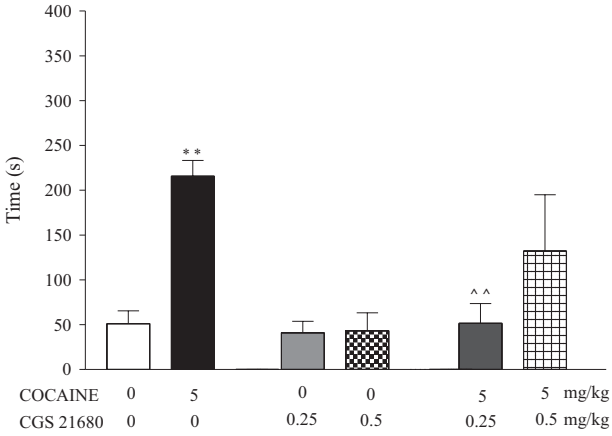

Fig. 2. The influence of CGS 21680 on the expression of CPP induced by cocaine; ** $p < 0.01$ compared to 0.9% NaCl, ^^ $p < 0.01$ – compared to cocaine

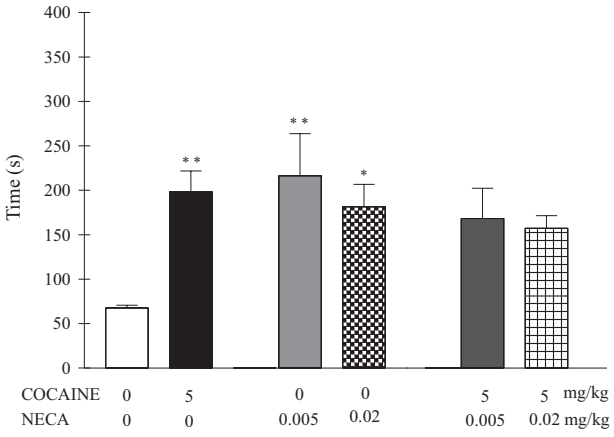

Fig. 3. The influence of NECA on acquisition of CPP induced by cocaine; ** $p < 0.01$, * $p < 0.05$ compared to 0.9% NaCl

preference produced by cocaine only at the lower dose used (0.005 mg/kg) (Fig. 4). Similarly as NECA, CPA given alone elicited a significant preference for a drug-associated (white) chamber during the cocaine-free post-test phase (Fig. 5). When CPA was paired with each injection of cocaine during the conditioning sessions, it did not influence the cocaine-induced acquisition of CPP (Fig. 5). At the lower dose, it attenuated the expression of the CPP induced by cocaine (Fig. 6).

The rats injected with DMPX alone (A2 antagonist) acquired neither preference nor aversion for the drug-associated (white) compartment of the apparatus (Fig. 7). DMPX did not influence the cocaine-induced acquisition (Fig. 7) but it reduced significantly expression of CPP (Fig. 8).

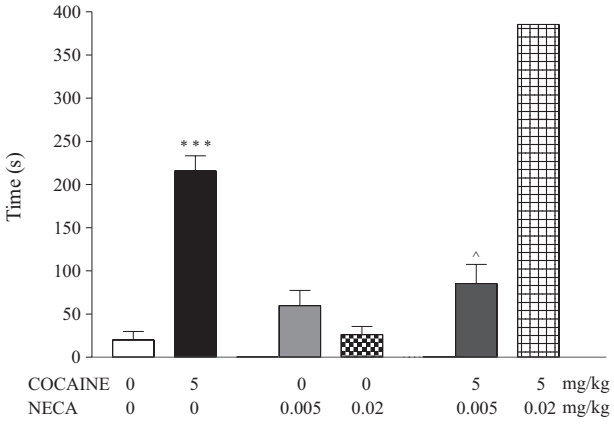

Fig. 4. The influence of NECA on expression of CPP induced by cocaine; *** $p < 0.001$ compared to 0.9% NaCl, ^ $p < 0.05$ compared to cocaine

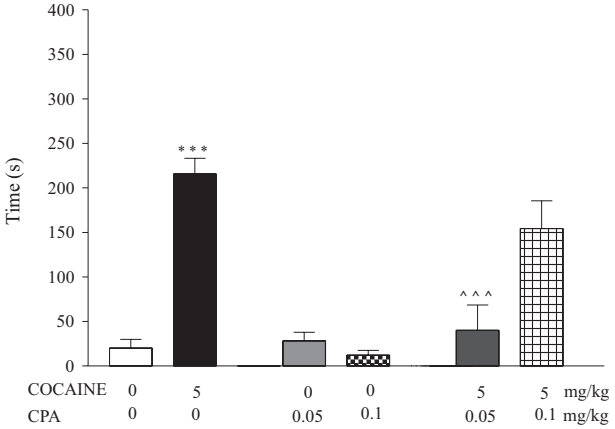

Fig. 6. The influence of CPA on expression of CPP induced by cocaine; *** $p < 0.001$ – compared to 0.9% NaCl, ^^^ $p < 0.001$ – compared to cocaine

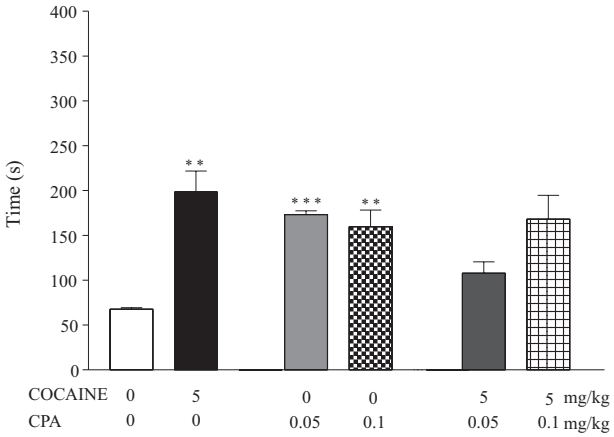

Fig. 5. The influence of CPA on acquisition of CPP induced by cocaine; *** $p < 0.001$, ** $p < 0.01$ – compared to 0.9% NaCl

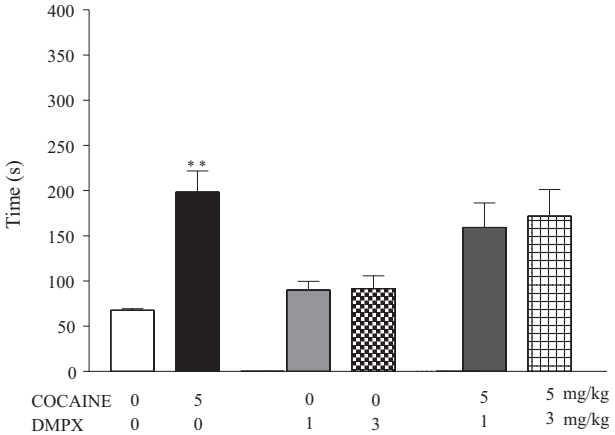

Fig. 7. The influence of DMPX on acquisition of CPP induced by cocaine; ** $p < 0.01$ – compared to 0.9% NaCl

CPT (selective A1 antagonist) given alone did not evoke the positive CPP (Fig. 9). Administered with each injection of cocaine during the conditioning sessions, it did not influence the action of cocaine (Fig. 9). Given as a single injection before the post-test phase to the rats previously conditioned with cocaine, it clearly prevented the expression of cocaine-induced CPP (Fig. 10).

Caffeine given alone, at doses of 10 and 20 mg/kg, had no rewarding properties (Fig. 11). Single injection of caffeine produced a similar action as it was observed after cocaine conditioning (Fig. 12). Caffeine (at the higher dose) attenuated the acquisition of cocaine-induced CPP (Fig. 11) and significantly and dose-dependently prevented the expression of the reaction (Fig. 12).

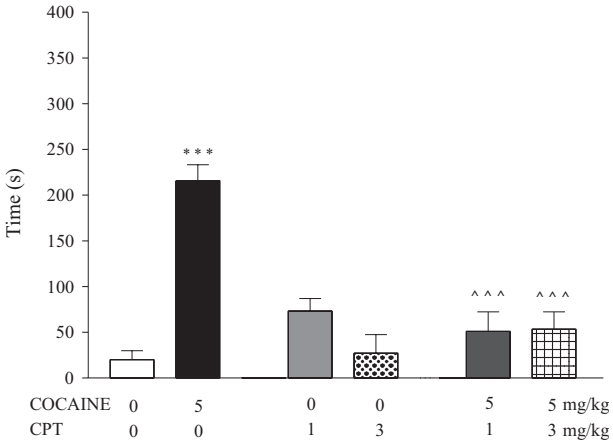

Fig. 10. The influence of CPT on expression of CPP induced by cocaine; *** $p < 0.001$ – compared to 0.9% NaCl, ^^^ $p < 0.001$ – compared to cocaine

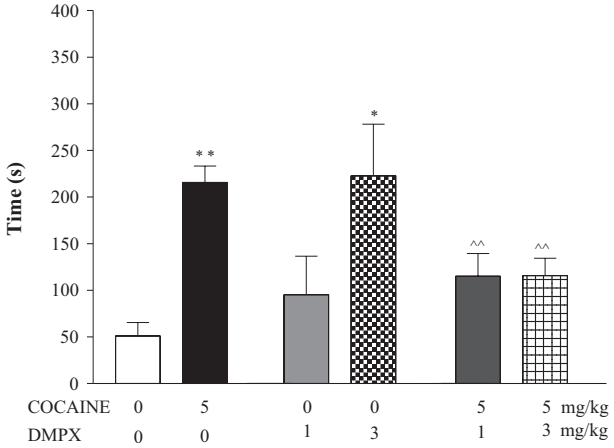

Fig. 8. The influence of DMPX on expression of CPP induced by cocaine; ** $p < 0.01$, * $p < 0.05$ – compared to 0.9% NaCl, ^^ $p < 0.01$ compared to cocaine

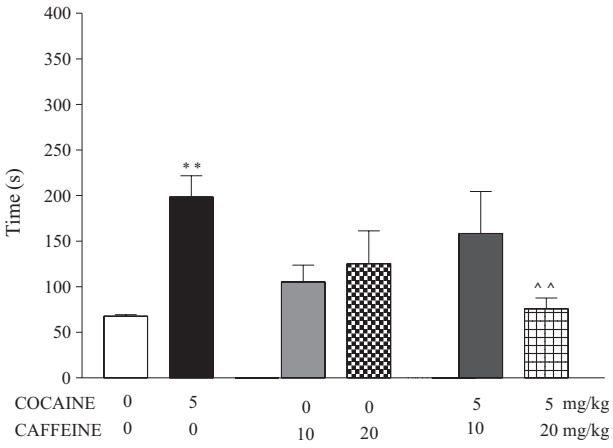

Fig. 11. The influence of caffeine on acquisition of CPP induced by cocaine; * * $p < 0.01$ – compared to 0.9% NaCl, ^^ $p < 0.01$ – compared with cocaine

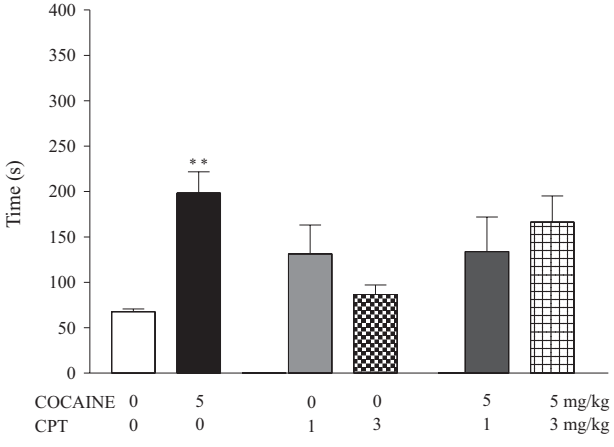

Fig. 9. The influence of CPT on acquisition of CPP induced by cocaine; ** $p < 0.01$ – compared to 0.9% NaCl

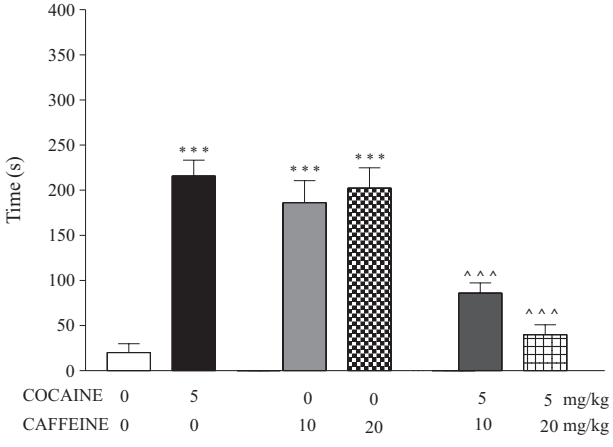

Fig. 12. The influence of caffeine on expresion of CPP induced by cocaine; *** $p < 0.001$ – compared to 0.9% NaCl, ^^^ $p < 0.001$ – compared to cocaine

The analyses of variance applied to for the effects of CGS 21680 on the acquisition and expression of CPP induced by cocaine, respectively, showed following effects ($F_{3,19}$: 13.50 $p < 0.0001$ and $F_{5,25}$: 6.23 $p = 0.007$); the effects of NECA ($F_{3,18}$: 6.31 $p = 0.004$ and $F_{5,27}$: 10.54 $p < 0.0001$); the effects of CPA ($F_{3,19}$: 15.40 $p < 0.0001$ and $F_{5,26}$: 21.22 $p < 0.0001$; effects of DMPX ($F_{3,19}$: 7.58 $p = 0.016$ and $F_{5,25}$: 4.86 $p = 0.031$); the effects of CPT ($F_{3,20}$: 8.08 $p = 0.001$ and $F_{5,26}$: 19.65 $p < 0.0001$); the effects of caffeine ($F_{3,18}$: 4.75 $p = 0.01$ and $F_{5,28}$: 24.10 $p < 0.0001$).

DISCUSSION

In line with the previous results [21], our study shows that cocaine at the dose of 5 mg/kg induced positive place preference in rats. Adenosine receptor agonists when given alone, induced also some positive response in CPP test: CPA at 0.05–0.1 mg/kg (A1 agonist) and A2/A1 receptor agonist NECA (0.005–0.02 mg/kg) produced place preference in rats, although the effects were not dose-dependent, but selective A2A receptor agonist, CGS 21680, elicited some place preference only at the lower dose used (0.25 mg/kg).

There are only few experiments in which the rewarding properties of adenosine receptor agonists and antagonists were evaluated. Brockwell and Beninger [4] have demonstrated in rats that A2 adenosine receptor antagonist CGS 15943A (9-chloro--2-(2-furanyl)-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-5-imine) dose-dependently produced place preference, but A1 receptor antagonist CPX (8-cyclopentyl-1.3-dipropylxanthine), A1 receptor agonist CPA (0.01–10 mg/kg) and A2 receptor agonist CGS 21680 (0.01–1 mg/kg) failed to produce significant place conditioning. Zarrindast and Moghadamnia [37] have shown that A1 adenosine receptor agonists: R-PIA (R-(2-phenylisopropyl)adenosine) and CHA (cyclohexyladenosine) induced conditioned place aversion in mice, whereas NECA evoked CPP.

Our experiments with NECA in acquisition test are consistent with the results of Zarrindast and Moghadamnia [37], but we have also observed that another selective adenosine A1 agonist, CPA and A2 receptor agonist CGS 21680 induced CPP in rats. It indicates that adenosine receptor agonists may induce place preference in some dose ranges. Such effects are similar to those induced by atypical neuroleptics in the food-induced CPP in rats [19], and indicate that adenosine receptors (probably both A1 and A2) may be involved in rewarding mechanisms.

Antagonist of adenosine A1 receptor CPT, given alone, had no influence in CPP test, and this our result is consistent with the observations of Brockwell and Beninger [4] on the effect of the other A1 antagonist – CPX. However, in our experiments, DMPX (A2 antagonist) did not produce a place preference, although the above authors observed it using CGS 15943A [4]. Some discrepancies between our findings and those of the above authors [4, 37] are probably the result of different experimental conditions: animals, doses, procedure of place preference.

The effects of adenosine receptor agonists on cocaine-induced CPP have not been examined as yet. In the recent experiments of Knapp et al. [23] with cocaine self-administration test, adenosine agonists NECA and CGS 21680 reduced the number of infusions in rats, and these results suggested that the administration of adenosine agonists may inhibit cocaine-seeking behavior. In the self-stimulation test, Baldo et al. [2] demonstrated that CGS 21680 diminished brain stimulation reward, whereas DMPX reversed the reward impairment produced by cocaine withdrawal. In our experiments, all adenosine receptor agonists did not prevent the acquisition of cocaine-induced CPP but, administered at the lower doses, they reduced the expression of cocaine action in this test. Our results in CPP test seem to partially (low doses of adenosine agonists, expression of CPP) agree with observations of Knapp et al. [23] with cocaine self-administration test, and those of Baldo et al. [2] with self-stimulation test, and they indicate that adenosine agonists may attenuate (in some dose ranges) the cocaine abstinence signs in animals.

Out of the group of adenosine receptor antagonists used in the present studies, CPT, DMPX and caffeine (at both doses used) markedly and significantly decreased the expression of CPP induced by cocaine, and caffeine (20 mg/kg) decreased also the acquisition of cocaine CPP. It means that adenosine A1 and A2 receptors are involved in rewarding properties of cocaine measured in CPP test. These results with adenosine antagonist are qualitatively similar to the effect observed with the low doses of adenosine agonists. It is not clear why these responses are similar. Perhaps reducing effects of low doses of adenosine agonists on the expression of

cocaine-induced CPP is a result of their sedative and antypsychotic properties [12, 25, 26, 31], although such effects are not observed with higher doses of adenosine agonists.

Reducing effects of adenosine receptor antagonists (CPT, DMPX and caffeine) on cocaine-induced CPP are clearly more visible. Their influence on the expression of cocaine-induced CPP is probably related to the fact that they may induce behavioral activity similar to cocaine action. Such possibility was suggested by other authors who investigated the interaction between cocaine and caffeine, for example Schenk et al. [33] have shown that caffeine is able to reinstate extinguished cocaine self-administration behavior in rats. Kuzmin et al. [24] demonstrated also that caffeine at 3 mg/kg, acting on adenosine A1 receptors, prevented the extinction of cocaine-seeking behavior in mice.

The influence of CPT and DMPX on cocaine-induced CPP was not investigated, but the interaction of caffeine with cocaine rewarding actions was studied by many authors, for example it has been shown that caffeine potentiated the discriminative stimulus and reinforcing effects of cocaine in laboratory animals [9, 18, 20, 22] and in humans [28].

Caffeine is a psychomotor stimulant and through its blocking action on adenosine A1 and A2 receptors, it influences indirectly dopaminergic system [13, 16]. For example, caffeine increases extracellular DA level through blockade of adenosine A1 receptors [27], and it was shown that D1 and D2 DA receptor antagonists blocked caffeine-induced stimulation of locomotor activity in rats [17]. Caffeine has some reinforcing properties in self-administration experiments in animals [1, 11]. Bedingfield et al. [3] have found that combination of low doses (0.3 mg/kg) of caffeine and cocaine has additive action which leads to the induction of CPP. In the CPP test, low doses of caffeine (1–3 mg/kg) are reinforcing [5, 30], but higher doses (20–30 mg/kg) are aversive [5, 34, 36]. In our experiments, we used doses of 10 and 20 mg/kg of caffeine, which were higher than those inducing reinforcement and nearly aversive. We did not observe marked effects in acquisition test, when caffeine was injected alone, but administration of these doses of caffeine reduced the expression of cocaine CPP, and after injection of caffeine (20 mg/kg) the acquisition of cocaine CPP was also diminished. Thus, caffeine may influence responding to cocaine in CPP test depending on the dose: lower doses of caffeine potentiate cocaine action, but higher doses may reduce cocaine-induced CPP. It means that probably higher doses of caffeine may attenuate development of cocaine dependence and withdrawal signs.

In summary, the present results have shown that adenosine receptor agonists may induce place preference in some dose ranges, and it seems that adenosine A1 and A2 receptors may be involved in this reaction. All adenosine receptor agonists did not prevent the acquisition of cocaine-induced CPP but, administered at the lower doses, they were able to diminish the expression of cocaine action in CPP test. Selective adenosine A1 antagonist, CPT, A2 antagonist, DMPX, and caffeine (non-selective A1/A2 receptor antagonist) markedly and significantly decreased the expression of CPP induced by cocaine, and caffeine (20 mg/kg) decreased also the acquisition of cocaine CPP.

Thus, all adenosine receptor antagonists were able to reduce the expression of cocaine CPP. It means that both adenosine receptors are involved in rewarding properties of cocaine in CPP test.

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