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Adenosine Receptor Agents and Conditioned Place Preference

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ABSTRACT. 1. The effects of different doses of the adenosine agonists N5-ethylcarboxamido-adenosine (NECA), R–isomer of N^6-phenylisopropyladenosine (R-PIA), and N^6-cyclohexyladenosine (CHA) or of the antagonists theophylline and 8-phenyltheophylline (8-PT) on conditioned place preference (CPP) have been studied.

2. The results show that R-PIA and CHA induced conditioned place aversion (CPA) whereas NECA induced conditioned place preference (CPP).

3. Low doses of theophylline elicit CPP, but high doses of the drug induced CPA. 8-PT also produced the CPP.

4. The responses of R-PIA and CHA but not NECA was decreased by theophylline and 8-PT administration.

5. It is concluded that the induction of CPP and CPA by adenosine antagonsists may be mediated by different adenosine receptors. GEN PHARMAC 29;2:285–289, 1997. **© 1997 Elsevier Science Inc.**

KEY WORDS. Conditioned place preference, conditioned place aversion, NECA, R-PIA, CHA, theophylline, 8-PT

INTRODUCTION

It is well established that adenosine is a neuromodulator in the central nervous system (Snyder, 1985). Adenosine agonists inhibit neuronal firing (Dunwiddie, 1985), reduce neurotransmitter release (Harms *et al.*, 1980; Myers and Pugsley, 1986), and influence neurotransmitter second messengers (Van Calker et al., 1979; Petcoff and Cooper, 1987). Analgesic, anticonvulsant, and hypnotic effects of adenosine receptors have been proposed (Dunwiddie and Worth, 1982; Yarbrough and McGuffin-Clineschmidt, 1981). Adenosine agonists also inhibit spontaneous locomotion (Barraco *et al.*, 1983; Snyder *et al.*, 1981; Vapaatlo *et al.*, 1975), and food intake (Levine and Morely, 1982).

The involvement of adenosine receptors in physiological functions is suggested by the high affinity for these receptors displayed by behaviorally active adenosine analogs (Bruns *et al.*, 1986), the lack of behavioral activity seen with analogs that lack adenosine receptor affinity (Taylor *et al.*, 1986), and the reversal of these effects by adenosine antagonists (Coffin *et al.*, 1984). The ability of centrally administered adenosine agonists to produce behavioral effects at doses that lack activity when administered systemically, combined with the reversal of such effects by adenosine antagonists (Barraco *et al.*, 1983), support the concept that certain behavioral effects of adenosine agonists are due to central actions. The inhibition of spontaneous and conditioned behaviors has been seen with adenosine agonists (Coffin *et al.*, 1984; Coffin and Spealman, 1985). Release of adenosine from the spinal cord (Sawynok *et al.*, 1989) and supraspinal areas (Sawynok *et al.*, 1991 may mediate a significant action of morphine. A major restricting factor in the clinical use of opioids is the fear of drug dependence (Weis *et al.*, 1983), which are known to induce behavioral reinforcing effects (Bilsky *et al.*, 1992). Three important neurochemical systems, opioid peptides, GABA, and dopamine have been investigated for rewarding. Opioid peptides and opiate drugs have rewarding properties (Di Chiara and North, 1992; Koob, 1992). Dopamine and GABA have also been implicating in rewarding induced by drugs (Koob, 1992). Our previous work showed that adenosine receptor activation may influence the antinociception induced by morphine (Zarrindast and Nikfar, 1994) and GABAergic drugs (Sabetkasai and Zarrindast, 1993). Adenosine agents can alter pecking in chickens (Zarrindast and Nasir, 1991), and yawning (Zarrindast and Poursoltan, 1989; Zarrindast *et al.*, 1995) and licking responses in rats (Zarrindast and Sharifzadeh, 1995) induced by the dopamine agonist apomorphine. Interactions between opioid and dopaminergic systems also have been shown. Morphine can inhibit yawning (Zarrindast and Jamshidzadeh, 1992) and ejaculation in rats (Zarrindast *et al.*, 1994) induced by dopamine D_2 receptor activation. Considering the interaction between responses induced by adenosine, opioid, GABA, and dopamine agents and the rewarding responses associated with opioid, GABA, and dopamine mechanisms (Di Chiara and North, 1992; Koob, 1992), evaluating the possible rewarding effects of different adenosine receptors is of interest. The present study was designed to determine the role of adenosine A_1 and A_2 receptors in conditioned place preference.

MATERIALS AND METHODS

Subjects

The subjects were male Swiss albino mice weighing 25–30 g at the start of experiment. They were housed 6 per cage and had free access to food and water.

Apparatus and training

The place preference apparatus and procedure are based on the method of Carr and White (1983) with a minor modification. Briefly, two large

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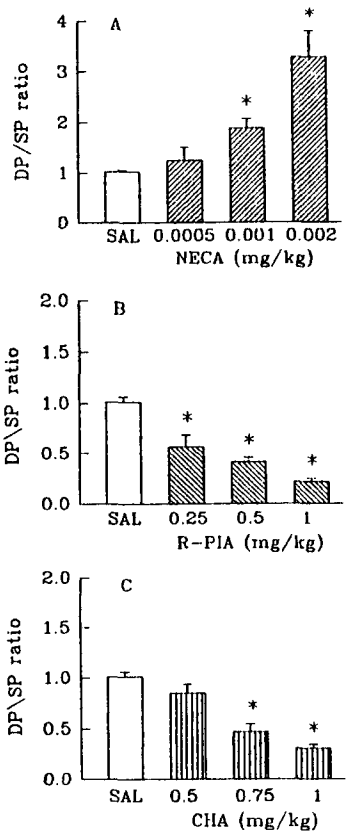

FIGURE 1. Adenosine agonist–induced place preference. Vertical axis, ratios of the time (sec) animals spent in drug-paired (DP) to saline-paired (SP) compartments on the test day. Hatched bars, ratios of different doses of NECA (A), R-PIA (B), or CHA (C). Open bars (control), ratios of times obtained when saline was injected in both compartments. Each value indicates the mean±SEM of DP/SP of 6 mice. *P<0.01 versus respective saline control group (Newman–Keuls test).

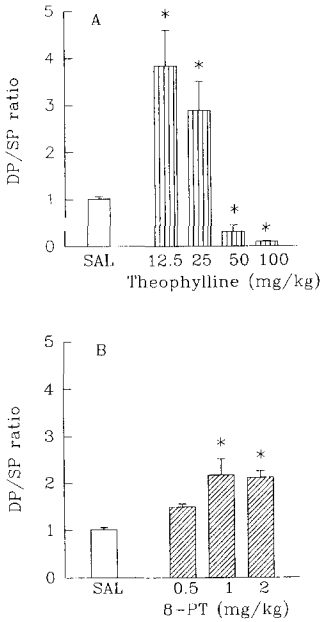

FIGURE 2. Adenosine antagonist–induced or –inhibited place preference. Vertical axis, ratios of the time (sec) animals spent in drug-paired (DP) to saline-paired (SP) compartments on the test day. Hatched bars ratios of different doses of theophylline (A) or, 8-PT (B). Open bars (control), ratios of times obtained when saline was injected in both compartments. Each value indicates the mean±SEM of DP/SP of 6 mice. *P<0.01 versus respective saline control group (Newman–Keuls test).

conditioning compartments A and B (30×30×30 cm) were connected by a communicating tunnel (compartment C; 25×15×30 cm) attached to one side. The conditioning compartments (A and B) were painted different colors (white and black). Access to the tunnel could be blocked by removable partition.

The conditioned place preference (CCP) procedure took place on 14 consecutive days. On day 1 (preexposure), each mouse was placed separately into the apparatus for 10 min, with free access to all compartments (A, B, and C). On the next 12 days, mice received 6 trials in which they experienced the effect of drug while confined in one compartment for 30 min, and 6 trials in which they received a saline injection and were confined to the other compartment. Access to compartment C (communicating tunnel) was blocked on these days. Drug and saline (IP) injections were on alternate days, 60 min prior to trials, and the order of presentation was counterbalanced. Each compartment was designated the drug side (drug-paired compartment) for half of the animals in each group. On day 14 (preference test), the communicating tunnel (compartment C) was opened, allowing access to all compartments. No injections were given; mice were place in the communicating tunnel. The relative amount of time the animals spent in each compartment during 20 min was the measure of the animal's preference. To compare the response induced by agonists or antagonists, the ratio of time spent in drug-paired (DP) to saline-paired (SP) compartments was recorded. DP/SP ratios are expressed as following:

$$\text{DP/SP Ratio} = \frac{\text{Time (sec) Spent in Drug-Paired Compartment}}{\text{Time (sec) Spent in Saline-Paired Compartment}}$$

DP/SP ratio=1 indicates no place preference (CPP) or place aversion (CPA). A DP/SP ratio larger than 1 indicates CPP induction, and a ratio smaller than 1 indicates CPA induction.

Drugs

The following drugs were obtained from Sigma (St. Louis, MO, USA): adenosine receptor agonists N^5-ethylcarboxamidoadenosine (NECA), N^6-phenylisopropyladenosine (R-PIA), and N^6-Cyclohexyladenosine (CHA); adenosine receptor antogonists theophylline and 8-phenyltheophylline (8-PT). (Jacobson *et al.*, 1992). All drugs were dissolved in 0.9% saline and administered (IP) (10 ml/kg).

Data analysis

An analysis of variance (ANOVA), followed by Newman–Keuls and Dunnett's tests, was performed. A difference with $P<0.05$ between experimental groups at each point was considered statistically significant.

RESULTS

Effects of adenosine receptor agonists on behavior in conditioned place preference paradigm

IP administration of different doses of NECA (0.0005, 0.001, and 0.002 mg/kg) to mice caused a significant and dose-related increase in time spent in the drug-paired compartment (DP) than that spent

TABLE 1. Effects of adenosine receptor agonists in presence or absence of adenosine receptor antagonists[a]

Pretreatment (mg/kg or ml/kg)	Treatment (mg/kg)	Time spent in treatment compartment (sec), mean ± SEM		DP/SP ratio[c]
		DP[b]	SP[b]	
Saline 10	NECA 0.001	588 ± 26.9	318 ± 19.7	1.86 ± 0.2
THEO 12.5	NECA 0.001	702 ± 15.4	312 ± 31.2	2.38 ± 0.4
8-PT 1	NECA 0.001	456 ± 27.6	264 ± 31.2	1.87 ± 0.3
Saline 10	NECA 0.002	758 ± 40.8	255 ± 28.8	3.25 ± 0.5
THEO 12.5	NECA 0.002	840 ± 19.2	237 ± 26.4	2.93 ± 0.2
8-PT 1	NECA 0.002	588 ± 43.2	241 ± 34.8	2.71 ± 0.5
Saline 10	R-PIA 0.25	254 ± 30.7	489 ± 49.0	0.44 ± 0.1
THEO 12.5	R-PIA 0.25	345 ± 18.4	372 ± 38.4	1.30 ± 0.2**
8-PT 1	R-PIA 0.25	446 ± 18.2	357 ± 33.6	1.31 ± 0.2**
Saline 10	R-PIA 0.5	149 ± 10.3	692 ± 36.0	0.36 ± 0.1
THEO 12.5	R-PIA 0.5	354 ± 26.4	372 ± 38.4	1.05 ± 0.2*
8-PT 1	R-PIA 0.5	521 ± 57.8	317 ± 39.6	1.47 ± 0.2**
Saline 10	CHA 0.5	351 ± 19.7	434 ± 33.6	0.82 ± 0.1
THEO 12.5	CHA 0.5	558 ± 19.2	295 ± 28.8	1.98 ± 0.2**
8-PT 1	CHA 0.5	408 ± 16.8	300 ± 15.8	1.36 ± 0.2**
Saline 10	CHA 1	194 ± 16.8	643 ± 43.2	0.48 ± 0.1
THEO 12.5	CHA 1	402 ± 28.8	192 ± 20.4	2.31 ± 0.5**
8-PT 1	CHA 1	477 ± 55.9	277 ± 19.2	1.69 ± 0.1**

[a] Mice were treated with NECA, R-PIA, and CHA in combination with saline theophylline (THEO) or 8-PT 20 min prior to administration of the agonists.

[b] Each piece of data indicates mean ± SEM of the time (sec) spent in drug-paired (DP) or saline-paired (SP) compartment.

[c] DP/SP ratios show the ratio of the time (sec) spent in drug-paired to saline-paired compartments. DP/SP ratio = 1 indicates no conditioned place preference (CPP), DP/SP ratio = more than 1 indicates increase in CPP, and DP/SP ratio = less than 1 indicate place aversion.

* $P < 0.05$, ** $P < 0.01$ versus respective control group.

in the saline-paired compartment (SP) ($F[3,20]=4.94$, $P<0.01$) (Fig. 1A). However, administration of R-PIA (0.25, 0.5, and 1 mg/kg IP) ($F[3,20]=13.31$, $P<0.01$) and CHA (0.5, 0.75, and 1 mg/kg IP) ($F[3,20]=24.15$, $P<0.01$) decreased the time spent in the DP compartment dose-dependently ($P<0.01$) (Figs. 1B and 1C).

Effects of adenosine receptor antagonists on behavior in conditioned place preference paradigm

Administration of different doses of theophylline to mice altered the time spent in DP compartment in a biphasic manner ($F[4,25]=4.18$, $P<0.01$). Low doses of the drug (12.5 and 25 mg/kg) induced CPP, but higher doses (50 and 100 mg/kg) produced (CPA) (Fig. 2A). The adenosine receptor antagonist 8-PT (0.5, 1, and 2 mg/kg, IP) induced CPP ($F[3, 20]=4.94$, $P<0.01$) (Fig. 2B).

CPP or CPA induced by adenosine agonists in the presence or absense of adenosine antagonists

Pretreatment of animals with theophylline (12.5 mg/kg IP) or 8-PT (1 mg/kg, IP) 20 min prior to NECA administration (0.001 and 0.002 mg/kg, IP) did not alter NECA-induced CPP ($F[5,30]=2.4$ $P<0.05$) (Table 1). However, administration of theophylline (12.5 mg/kg, IP) or 8-PT (1 mg/kg,IP) 20 min prior to R-PIA administration (0.25 and 0.5, IP) antagonized R-PIA– induced CPA ($F[5,30]=7.5$, $P<0.01$). The same doses of theophylline and 8-PT 20 min prior to CHA (0.5 and 1 mg/kg, IP) antagonized CHA-induced CPA dose–dependently ($F[5,30]=8.1$, $P<0.01$).

DISCUSSION

The present study indicates that adenosine receptor agonists and antagonists can alter time that mice spent in the DP compartment. The adenosine receptor agonists R-PIA and CHA induced CPA, and NECA induced CPP. Opioid peptides and morphine have been shown to be rewarding (Di Chiara and North, 1992; Koob, 1992). GABA and dopamine mechanisms also have been implicated in rewarding induced by drugs (Koob, 1992). Adenosine agents also may have an influence on the antinociceptive responses induced by morphine (Zarrindast and Nikfar, 1994), GABA (Sabetkasai and Zarrindast, 1993), and on the behavioural effects induced by dopaminergic agents (Zarrindast and Nasir, 1991; Zarrindast and Poursoltan, 1989; Zarrindast *et al.*, 1995; Zarrindast and Sharifzadeh, 1995). Thus the data may suggest that adenosine mechanisms are rewarding. NECA, which induced CPP in the present experiment, increases morphine antinociception (Zarrindast and Nikfar, 1994). The data also indicate that the adenosine receptor antagonists theophylline (Daly 1982; Choi *et al.*, 1988) and 8-PT (Smellie *et al.*, 1979) interact with CPP. Low doses of the receptor antagonist theophylline induced CPP, but high doses of the drug produced CPA. 8-PT also can induce CCP. It should be considered that theophylline decreases morphine antinociception, whereas 8-PT increases it (Zarrindast and Nikfar, 1994). It remains to be clarified whether morphine rewarding induced by adenosine mechanism(s) or the possible rewarding responses of NECA and adenosine antagonists are mediated by the opioid system. However, the antinociceptive response of morphine has been shown to be due to adenosine mecha-

nism(s) (Sawynok *et al.*, 1989). R-PIA– or CHA-induced CPA was abolished by low doses of theophylline and 8-PT, but theophylline and 8-PT did not alter NECA-induced CPP. However, the antogonists' own influence on CPP also should be considered. These effects may further support the fact that adenosine mechanism is involved in rewarding. High-affinity adenosine receptors of the A_1 and A_2 subtypes mediate different physiological actions of adenosine, display distinct stucture–activity relationships, and are distributed differentially in tissues, including the brain (Bruns *et al.*, 1980; Hamilton *et al.*, 1987; Londos *et al.*, 1980; Van Calker *et al.*, 1979). The relative potency for A_1 adenosine receptors has been suggested to be CHA>R-PIA>NECA and NECA>R-PIA>CHA for A_2 adenosine receptors (Heffner *et al.*, 1989). R-PIA and CHA have more affinity for A_1 adenosine receptors. Therefore, one may suggest that CPA Induced by these drugs may be mediated by an A_1 adenosine receptor mechanism. Because high doses of theophylline that may act as phosphodiesterase inhibitor (Choi *et al.*, 1988) even induced CPA in the present study, NECA-induced CPP cannot be mediated through an elevation in cAMP. The same doses of NECA that we used did not affect locomotion either. Thus, the locomotion seems to play no role in the NECA response. NECA has an appreciable affinity for A_2 adenosine receptors (Heffner *et al.*, 1989) that can be altered by theophylline or 8-PT. This may suggest that CPP induced by NECA is related to the A_2 adenosine receptor subtype.

Whereas A_1 adenosine receptors are widely distributed in the brain, A_2 adenosine receptors are highly localized within dopamine-rich brain areas such as the corpus striatum, nucleus accumbens, and olfactory tubercle (Bruns *et al.*, 1986).

The dopaminergic mechanisms have been demonstrated to be involved in CPP (Aulisi and Hoeble, 1983; Carr and White, 1983; Spyraki *et al.*, 1982). Considering the inhibition of dopamine release from central neurons by adenosine agonists (Harms *et al.*, 1980; Myers and Pugsley 1986) and also the involvement of the mesolimbic dopaminergic systems in positive reinforcing response due to some drugs as also proposed by other researchers (Spanagel *et al.*, 1991), it may be that the effects of the adenosine agonists are mediated through a dopaminergic reward system in the central nervous system. However, the exact mechanism involved remains to be elucidated. On the other hand, methylxanthines such as theophylline can potentiate the effect of endogenous dopamine in postsynaptic D_2 stimulation through A_2 antagonism (Ferre *et al.*, 1991). The increase in CPP by low doses of theophylline may be mediated through dopaminergic mechanism(s). High doses of theophylline that act as a phosphodiesterase inhibitor (Choi *et al.*, 1988) decrease the DP. Because NECA has more affinity for A_2 (Hefner *et al.*, 1989), which may elevate cAMP levels, and increase the CPP, the involvement of cAMP in the response of theophylline seems unlikely. Further investigations with more specific adenosine agents for subtypes of A_1 and A_2 receptors may be needed to show the exact mechanism involved.

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