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Adenosine A_2 receptors inhibit morphine self-administration in rats

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Abstract

In the present study, the effect of adenosine receptor agonists and antagonists on morphine self-administration was investigated. Intravenous administration of morphine (0.3–3 mg/kg/injection) induced dose-dependent self-administration. The adenosine receptor antagonists, theophylline (2.5, 5, 10 mg/kg) and 3,7-Dimethyl-1-propargylxanthine (DMPX; 0.25, 0.5, 1 mg/kg), when injected 1 h before the start of the test, reduced the number of self-administered morphine infusions. The adenosine receptor antagonists when administered in the training period (11 days) greatly increased the number of morphine infusions, however, they did not induce any response by themselves. 5′-*N*-ethylcarboxamido-adenosine (NECA; 0.5, 1 mg/kg) and 4-[2-[[6-Amino-9-(*N*-ethyl-β-D-ribofuranuronamidosyl)-9H-purin-2-yl]amino] ethyl]benzenepropanoic acid (CGS21680; 0.001, 0.01, 0.025, 0.05 mg/kg), given 1 h before the start of the test, increased morphine self-administration. Although the adenosine agonists, when injected during training period (11 days), reduced morphine self-administration. Furthermore, NECA, but not CGS21680, induced significant self-administration. The adenosine A_1 receptor agonist, N^6-cyclohexyladenosine (CHA; 0.01, 0.1, 0.25, 0.5 and 1 mg/kg), and the adenosine A_1 receptor antagonist, 8-phenyletheophylline (2, 4, 6, 8 mg/kg), themselves neither altered morphine infusion nor induced any response. These results indicate a role for adenosine A_2 receptors in the expression and/or development of morphine self-administration.

Keywords: Morphine self-administration; Adenosine receptor agonist; Adenosine receptor antagonist

1. Introduction

Adenosine is an important neuromodulator in the central nervous system (CNS) (Dunwiddie, 1985). Specific receptor sites for adenosine have been demonstrated within the areas of the CNS (Lee and Reddington, 1986). A great number of research findings indicate that adenosine receptors have a role in mediating opiate effects (Kaplan and Sears, 1996). Acute morphine treatment enhances the central release of adenosine, and opiate antagonist inhibits this release (Phillis et al., 1979). Adenosine receptor agonist treatment may alter (Zarrindast and Nikfar, 1994), or even potentiate morphine antinociception in animal models (Contreras et al., 1990) and in humans (Segerdhal et al., 1994). There are several studies that demonstrate that adenosine receptor agonists and antagonists influence the development of opiate tolerance and withdrawal. Some adenosine receptor agonists inhibit the development of tolerance to opiate analgesia (Ahlijanian and Takemori, 1985; Germany et al., 1990), and expression of opiate withdrawal (Tucker et al., 1984; Dionyssopoulos et al., 1992). The adenosine system has also been implicated in conditioned place preference (Zarrindast and Moghadamnia, 1997), however, there is little evidence for possible effects of the adenosine system on morphine self-administration. In this study the influence of some adenosine receptor agonists and antagonists on morphine self-administration was investigated.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Pasture Institute, Tehran, Iran), weighing 270–320 g at the beginning of the study were used in these experiments. The animals were housed

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in groups of 5–6 in plastic cages, allowed free access to food and water and maintained on a 12-h light–dark cycle (lights on 1900–0700) and constant temperature (22 ± 2°C). Eight animals were used in each experiment. Each animal was used only once.

2.2. Surgical procedure

The surgical procedure was based on the work described by Van Ree et al. (1978). Each animal was anaesthetized with sodium pentobarbital (50 mg/kg, i.p.) and surgically prepared with a chronic jugular cannula of silicone rubber (0.62 mm inner diameter, 1.0 mm outer diameter). The tip of the cannula was occluded with silicone adhesive (Silastic, Razi Chemical, Iran) and a series of small holes was made near the tip with a sharp needle. This cannula prevents contact between blood and infusion fluid, until fluid pressure in the lumen of the cannula during infusion expands the tubing and opens the holes (Davis, 1966). The cannula was inserted into the vein where its tip was located near the right atrium, its free end was guided subcutaneously to the skull and connected to polyethylene tubing by a U-shaped stainless steel tube which was fixed to the skull with dental acrylic cement and two screws. After surgery, the animals were placed in individual cages and were allowed 5 days for recovery from the operation. During testing the availability of food was restricted in order to reduce body weights by 15%, which has been shown to facilitate the initiation of intravenous self-administration (De Vry et al., 1989). The animals were tested in the dark phase of the light cycle.

2.3. Self-administration apparatus

Training and testing were done in a standard operant conditioning cage placed in a sound-attenuated room ventilated with fans. The test cages were equipped with two levers, one of which was marked by a red light placed just above the lever. The i.v. cannula of the animal was connected to an infusion pump via a swivel, allowing the animal to move relatively freely. Pressing of the lever marked by the red light (reinforcement lever) resulted in a 15-s infusion of 0.1 ml fluid through an infusion pump (Razel). The red light went off during the infusion and pressing the lever during this time did not result in an infusion action. Pressing of the other lever (non-reinforcement lever), which did not yield any response, also was recorded. In this self-administration model the number of infusions is regarded as a measure of the reinforcing action of the drug.

2.4. Self-administration procedure

Five days after surgery the rats were prepared for training. The animals were brought to a room with reversed day/night cycle (dark period, 0700–1900). The experiments were conducted over 12 days and in three sections.

2.4.1. Forced injection period

For induction of self-administration, the animals were placed in the test cages and a saline solution of morphine was injected daily at 30-min intervals for 2-h, for a period of 4 days (20-s injection of 0.5 ml solution). During this period, the dose of morphine was doubled every day.

2.4.2. Training period

From the fifth day onward, the forced opioid injection was discontinued and the animals were given free access to the levers for 7 days. The amount of drug infused per injection in this period was the same as in the first day of the forced injection period. Changes of less than 15% in the number of injections in the last 3 days were recorded and used as baseline. Thus, the number of injections was constant and tolerance did not appear.

2.4.3. Test day

On day 12, the animals were placed in the cages and the number of lever pressings was recorded as an indicator of drug self-administration.

To test the effects of the adenosine drugs on the expression of morphine self-administration, once baseline rates of morphine self-administration were established (a suitable baseline was achieved when the animals showed a less than 15% difference between the numbers of self-administrations in the last three successive days), saline or various doses of adenosine agents were injected (i.p.) before testing. The animals which did not show a stable self-administration pattern were disregarded.

The effects of various doses of adenosine agents injected (i.p.) during the training and forced injection periods (1 h before starting each session) were investigated to examine whether adenosine agents themselves can induce self-administration (procedure same as for morphine).

2.5. Drugs

The following drugs were used in these experiments: Morphine sulfate (TEMAD, Iran); theophylline, 8-phenyltheophylline, N^6-Cyclohexyladenosine (CHA) and N^5-Ethyl carboxamidoadenosine (NECA) (Sigma, LaJola, CA, USA); 3,7-Dimethyl-1-propargylxanthine (DMPX) and 4-2-[[6-Amino-9-(*N*-ethyl-β-D-ribofuranuronamidosyl)-9H-urin-2-yl]amino] ethyl]benzenepropanoic acid (CGS21680) (Research Biochem., USA). The drugs were dissolved in sterile saline solution except theophylline, which was dissolved in an alkaline solution and CGS21680 was dissolved in 40% DMSO (dimethylsulfoxide). 8-Phenyltheophylline was dissolved in a drop of ethylenediamine and then diluted with saline. The pH of the drug solutions was

adjusted to 7.40. The drugs were given intraperitoneally in a volume of 1 ml/kg and were prepared immediately before use. The control groups received saline or DMSO (40%).

2.6. Data analysis

Analysis of variance (one-way ANOVA) followed by Tukey protected *T* tests was used for statistical analysis. A

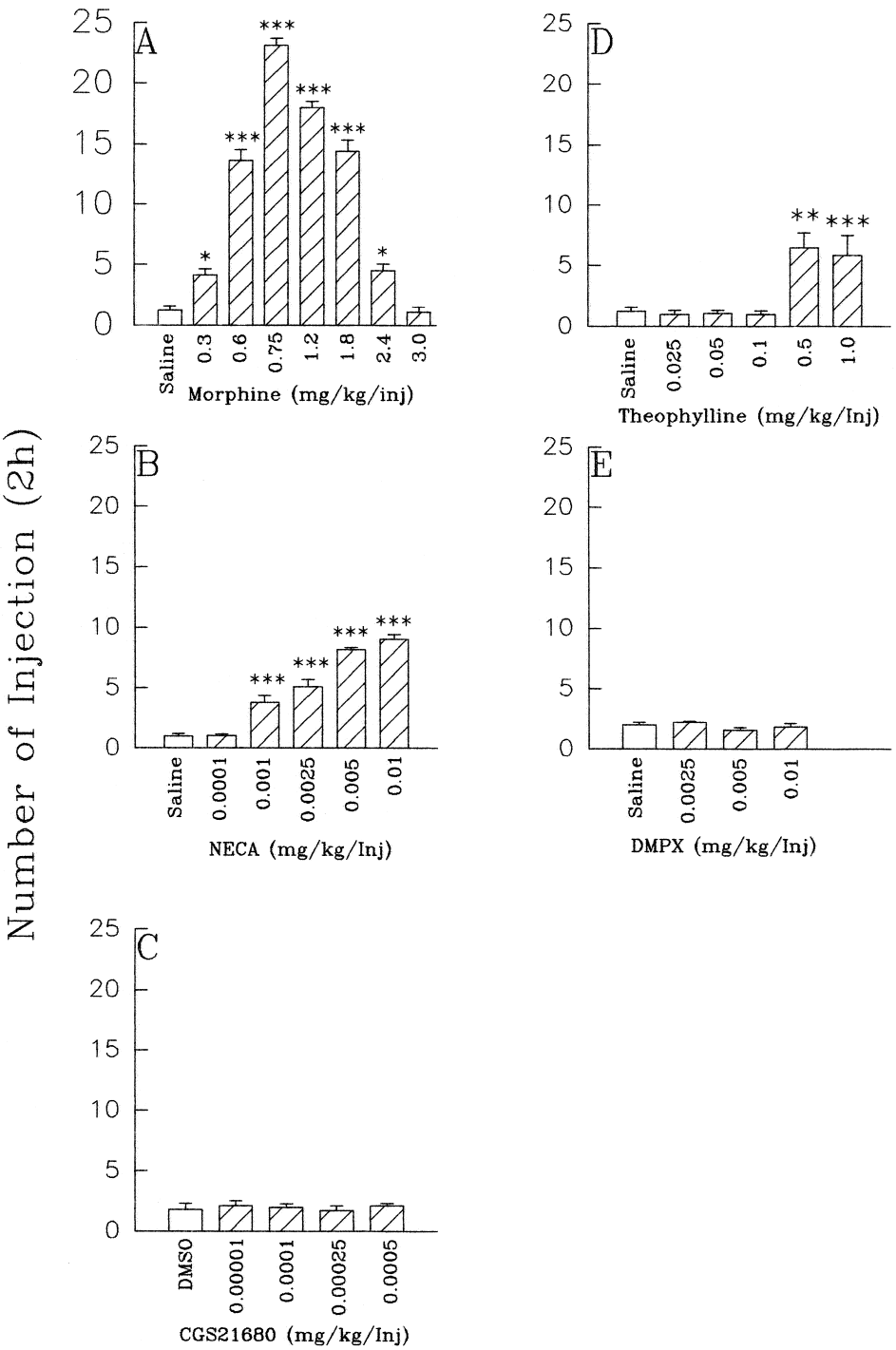

Fig. 1. Self-administration of morphine and adenosine receptor agents by rats. Animals were given the opportunity to self-administer different doses of morphine (A; 0.3–3 mg/kg/injection), NECA (B; 0.0001–0.01 mg/kg/injection), CGS21680 (C; 0.00001–0.0005 mg/kg/injection), theophylline (D; 0.025–1 mg/kg/injection) and DMPX (E; 0.0025–0.01 mg/kg/injection) for a period of 2 h (as described in Materials and methods). Each point is the mean ± S.E.M. for eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ different from respective saline or vehicle control group.

difference of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Self-administration behavior with morphine and adenosine receptor agonists and antagonists

Fig. 1 shows the self-administration induced by morphine, NECA, CGS21680, theophylline and DMPX. When rats were given the opportunity to self-administer, the number of saline self-administrations was 1–3 injections, after a period of training (a unit volume of 0.1 ml = one injection). In contrast, the animals which were given the opportunity to self-administer different doses of morphine (0.3–3 mg/kg/injection) in a period of 2 h, achieved self-administration in a dose-dependent manner. The maximum response was obtained with 0.75 mg/kg/injection. However, when animals were given the opportunity to self-administer higher doses of the opioid, the number of injections was reduced [$F(7,56) = 181$, $P < 0.0001$] (Fig. 1A). A dose of 0.75 mg/kg/injection was chosen as maximum dose in subsequent experiments.

With the same procedure which was used for morphine self-administration, NECA [$F(5,42) = 71.5$, $P < 0.0001$) (Fig. 1B) but not CGS21680 [$F(4,35) = 0.24$, $P > 0.05$] (Fig. 1C) also elicited self-administration. ANOVA indicated that single administration of different doses of theophylline (0.025–1.0 mg/kg/injection) [$F(5,42) = 11.1$, $P < 0.0001$] induced self-administration (Fig. 1D). Further analysis showed that higher doses of the drug (0.5 and 1.0 mg/kg/injection) caused self-administration. DMPX administration (0.0025, 0.005 and 0.01 mg/kg/injection) did not induce self-administration [$F(3,28) = 1.42$, $P > 0.05$] (Fig. 1E). CHA [$F(5,42) = 0.44$, $P > 0.05$], and 8-phenyltheophylline [$F(4,35) = 0.51$, $P > 0.05$] did not induce any response either (data not shown).

3.2. Influence of adenosinergic compounds on acquisition of morphine self-administration

Fig. 2 shows the effects of adenosine receptor agonists and antagonists on morphine self-administration. Intraperi-

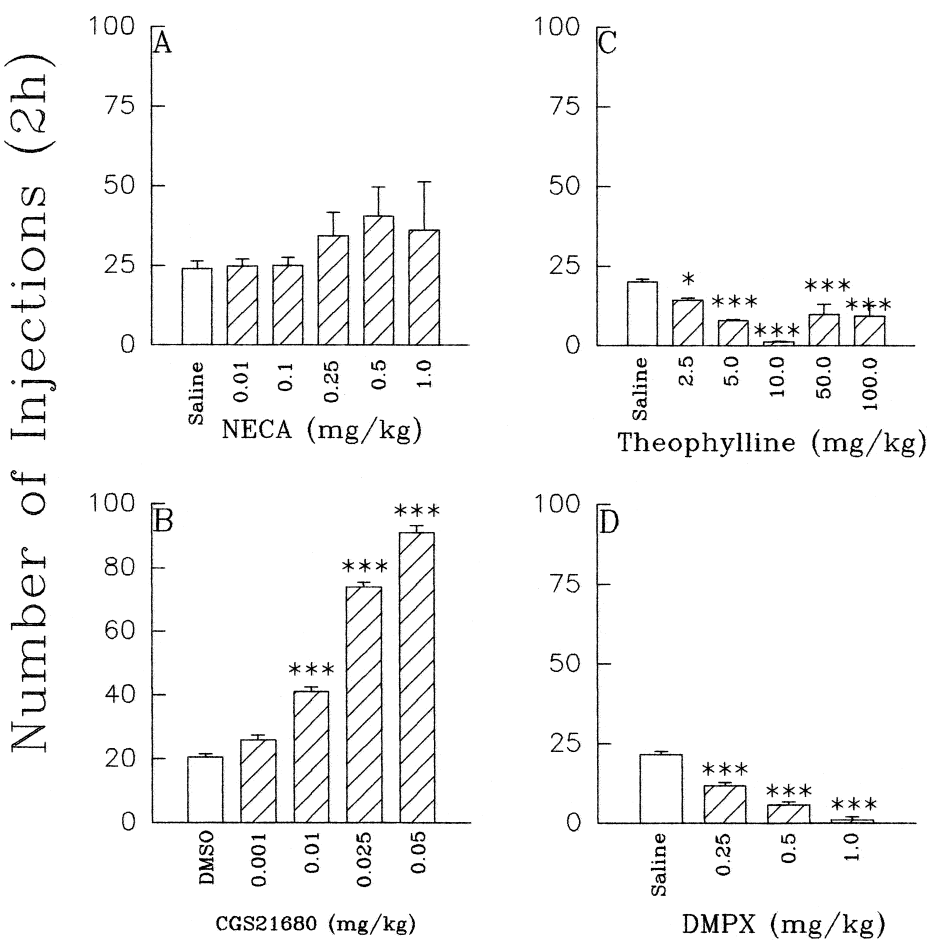

Fig. 2. Effect of different doses of adenosine receptor agonists or antagonists on acquision of morphine self-administration. Animals were injected with NECA (A), CGS21680 (B), theophylline (C), or DMPX (D), 1 h before the test and were given the opportunity to self-administer morphine for 2 h. Each point is the mean ± S.E.M. for eight animals. $^{*}P < 0.05$, $^{***}P < 0.001$ different from respective saline or vehicle control group.

toneal (i.p.) administration of NECA (0.01, 0.1, 0.25, 0.5 and 1 mg/kg) [$F(5,42) = 0.79$, $P > 0.05$] (Fig. 2A) did not produce any effect, while administration of CGS21680 (0.001, 0.01, 0.025 and 0.05 mg/kg; i.p.) [$F(4,35) = 373.8$, $P < 0.0001$] (Fig. 2B) 1 h before the test, increased morphine self-administration. Administration of theophylline (2.5, 5, 10, 50 and 100 mg/kg, i.p.) [$F(5,42) = 10.5$, $P < 0.0001$] (Fig. 2C) or DMPX (0.25, 0.5 and 1 mg/kg, i.p.) [$F(3,28) = 78.5$, $P < 0.0001$] (Fig. 2D) 1 h before the test, decreased morphine self-administration. Neither CHA (0.01–1 mg/kg, i.p.) [$F(5,5) = 0.0046$, $P > 0.05$], nor 8-PT (2–8 mg/kg, i.p.) $F(4,4) = 0.27$, $P > 0.05$], when administered 1 h before the test, altered the number of morphine injections (data not shown).

3.3. Influence of adenosinergic compounds on maintenance of morphine self-administration

Administration of NECA (0.01, 0.1, 0.25, 0.5 and 1 mg/kg, i.p.) [$F(5,42) = 8.4$, $P < 0.0001$] (Fig. 3A) or CGS21680 (0.001, 0.01, 0.025 and 0.05 mg/kg) [$F(4,35) = 31$, $P < 0.0001$] (Fig. 3B), 1 h before training (during the training days), altered morphine self-administration. Further analysis showed that CGS21680 and the higher doses of NECA (0.5 and 1 mg/kg) reduced morphine self-administration.

Administration of theophylline (2.5, 5, 10, 50 and 100 mg/kg, i.p.) [$F(5,42) = 7.2$, $P < 0.0001$] (Fig. 3C) or DMPX (0.25, 0.5 and 1 mg/kg, i.p.) [$F(3,28) = 393$,

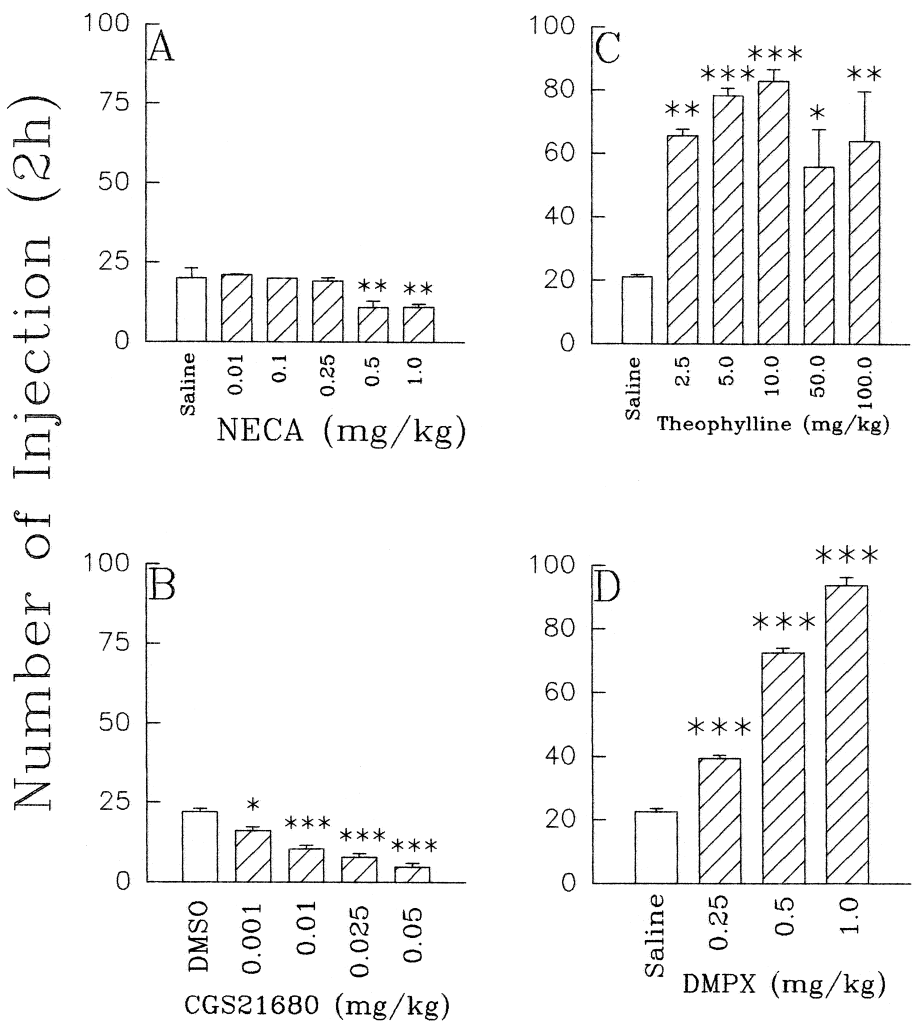

Fig. 3. Effect of different doses of adenosine receptor agonists or antagonists on maintenance of morphine self-administration. Animals were injected with NECA (A), CGS21680 (B), theophylline (C), or DMPX (D), 1 h before training (for 11 days) and were given the opportunity to self-administer morphine for 2 h on the test day. Each point is the mean ± S.E.M. for eight animals. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ different from respective saline or vehicle control group.

$P < 0.0001$] (Fig. 3D) 1 h before training (during the training days) increased morphine self-administration. CHA [$F(5,5) = 0.83$, $P > 0.05$] or 8-phenyltheophylline [$F(4,4) = 0.98$, $P > 0.05$] administered 1 h before training did not change morphine self-administration (data not shown).

4. Discussion

The effect of the adenosine system on morphine self-administration has not been studied earlier. Many studies have described a role for adenosine and adenosine receptors in mediating opiate dependence (Ahlijanian and Takemori, 1985, 1986; Kaplan and Sears, 1996). The present study concerned the effects of adenosine agents on morphine self-administration. The results indicated that adenosine receptor agonists and antagonists both alter morphine self-administration, suggesting that adenosine receptors may be involved in morphine self-administration and/or reward mechanism(s). Adenosine acts through different receptor sites, namely adenosine A_1 and A_2 receptors. Activation of adenosine A_1 and A_2 receptor subtypes inhibits or stimulates adenylyl cyclase activity, respectively (Van Calker et al., 1979; Londos et al., 1980). However, recently, adenosine receptors have been divided into subtypes known as A_1, A_2, A_3 and A_4 receptor types (Dalziel and Westfall, 1994; Fredholm et al., 1994). Our data showed that low doses of theophylline, an adenosine A_1/A_2 receptor antagonist (Bruns et al., 1986), when administered 1 h before the test, reduced morphine self-administration. Our previous study had shown that theophylline is able to decrease morphine antinociception (Zarrindast and Nikfar, 1994). Since theophylline may have more affinity for adenosine A_2 receptors (Daly et al., 1983; Ferré et al., 1991), the involvement of an adenosine A_2 receptor mechanism in the response elicited by theophylline seems likely. The selective adenosine A_2 receptor antagonist, DMPX (Seale et al., 1988), also reduced morphine self-administration, a finding which supports A_2 involvement. This hypothesis is also supported by other results of experiments which indicated that, on the contrary, CGS21680, a selective adenosine A_2 receptor agonist (Phillis, 1990), when administered 1 h before the test, increased morphine self-administration. Theophylline may elicit the release of dopamine (Lin et al., 1980), since dopamine receptor activation induces reward, this mechanism cannot account for the inhibition of morphine self-administration by theophylline. Theophylline is also a phosphodiesterase inhibitor at high doses (Choi et al., 1988) and an increase in the cAMP levels may be involved in reward (Nestler, 1992). Since the doses of theophylline which were used in the present study were low (2.5, 5 and 10 mg/kg), the possibility of an increase in the cAMP level in the response to theophylline seems unlikely. On the contrary, higher doses of theophylline (50 and 100 mg/kg) themselves produced self-administration and reversed morphine self-administration when compared with the effect of lower doses of the drug, indicating an influence of a response to both higher and lower doses of theophylline. The data indicate that adenosine A_2 receptor inhibition may be involved in the expression of morphine self-administration, and the response induced by higher doses of theophylline may be due to dopamine release (Lin et al., 1980). Regarding an involvement of the mesolimbic dopaminergic system in morphine self-administration, our results are consistent with the hypothesis that the distribution of adenosine A_2 receptors in the CNS is relatively restricted to the limbic region (Premont et al., 1979); interestingly, the A_{2A} subtype is colocalized with D_2 dopamine receptors on dopaminergic terminals in this region (Ferré et al., 1992). A link between adenosine A_2 and dopamine D_2 receptors has also been proposed by some investigators (Ferré et al., 1992). Therefore, the release of dopamine or A_2 activation by CGS21680 may have been involved in increasing morphine self-administration in the present study.

That NECA per se can also cause self-administration is in agreement with our previous report showing that NECA can induce conditioned place preference (Zarrindast and Moghadamnia, 1997). Since CGS21680 does not act like NECA, the increase in self-administration caused by NECA may not be due to adenosine A_2 receptor activation. The mechanism is unclear at the moment and needs further investigation. Administration of NECA or CGS21680, 1 h before training, (during a period of 11 days), reduced, while theophylline or DMPX increased, morphine self-administration, indicating an inhibition of the development of reward processes, possibly due to adenosine A_2 receptor activation. Considering the decrease in the number of injections at the higher doses of morphine (Fig. 1A), one may also conclude that the responses elicited by NECA or CGS21680 are possibly mediated through an increase in morphine potency. Decreases in striatal adenosine A_{2A} receptor concentrations and reduced A_{2A}-mediated adenylate cyclase activity have also been shown in morphine-dependent rats (De Montis et al., 1992). Thus, a possibility may exist that chronic activation or blockade of adenosine A_2 receptors mediates a decrease or increase in the development of reward processes by altering receptor numbers and/or cAMP levels. Furthermore, the effects of the adenosine receptor agents, which do not seem to be dose-related in some cases, may be due to possible indirect effects of the agents or to interactions of different systems in the self-administration behavior. However, to clarify the exact mechanism involved may require more experiments.

Increases in adenosine A_1 receptor numbers (Ahlijanian and Takemori, 1986) and enhancement of adenosine A_1 receptor affinity (Kaplan et al., 1994) have also been found in brain tissues of morphine-dependent mice. It was shown that chronic morphine treatment increases the analgesic effects of adenosine receptor agonists without altering cortical adenosine A_1 receptor number, suggesting recep-

tor sensitization (Tao and Liu, 1992). However, neither the adenosine A_1 receptor agonist, CHA (Moos et al., 1985), nor an adenosine A_1 receptor antagonist, 8 phenyltheophylline (Smellie et al., 1979; Jacobson et al., 1985), had any influence on morphine self-administration in the present study, indicating that adenosine A_1 receptors may not be involved in morphine self-administration in rats.

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