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Effects of adenosine receptor agents on the expression of morphine withdrawal in mice

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Abstract

Effects of different doses of adenosine receptor agonists and antagonists on naloxone-induced jumping and diarrhea in morphine-dependent mice were studied. The adenosine A_1 receptor agonists, N^6-cyclohexyladenosine (CHA: 0.1, 0.25 and 0.5 mg kg^{-1}) and *R*-isomer of N^6-phenylisopropyladenosine (R-PIA: 0.1, 0.3 and 1 mg kg^{-1}), decreased jumping and diarrhea induced by naloxone in morphine-dependent mice. The adenosine A_1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX: 0.3–9 mg kg^{-1}), increased jumping but decreased diarrhea. The adenosine A_2 receptor agonist, 5′-(*N*-cyclopropyl)-carboxamidoadenosine (CPCA), decreased jumping and diarrhea. However, the adenosine A_2 receptor antagonist, 3,7-dimethyl-1-propargylxanthine (DMPX: 0.5 and 1 mg kg^{-1}), did not elicit any response in this respect. DPCPX (0.3 and 3 mg kg^{-1}), decreased the inhibition of jumping and diarrhea induced by CHA (0.5 mg kg^{-1}), while DMPX (0.5 and 1 mg kg^{-1}), decreased the inhibition of diarrhea induced by CPCA (0.1 mg kg^{-1}). It is concluded that jumping induced by naloxone in morphine-dependent mice may be modified by the adenosine A_1 receptor mechanism(s) and diarrhea induced by the opioid receptor antagonist could be mediated by the adenosine A_1 and A_2 receptors.

Keywords: Jumping; Diarrhea; Morphine; Naloxone; Adenosine; (Mouse)

1. Introduction

Adenosine is a neuromodulator in the central nervous system (Bundege and Dunwiddie, 1997). Adenosine receptor sites are called A_1, A_2, A_3 and A_4 receptors (Dalziel and Westfall, 1994; Fredholm et al., 1994). High affinity adenosine receptors of the A_1 and A_2 subtypes mediate different physiological actions of adenosine, display distinct structure–activity relationships and are distributed differently in tissues, including the brain (Olah and Stiles, 1995). Adenosine receptor agonists inhibit neuronal firing (Dunwiddie, 1985), reduce neurotransmitter release (Harms et al., 1979; Myers and Pugsley, 1986) and influence neurotransmitter second messengers (Dalziel and Westfall, 1994). Analgesic, anticonvulsant and hypnotic effects of adenosine receptors have been proposed (Yarbrough and McGuffin-Clineschmidt, 1981). Our previous study also showed that adenosine receptor activation may alter animals' behaviours (Zarrindast et al., 1996), influence the antinociception induced by GABA receptor agonists (Sabetkasai and Zarrindast, 1993) and stress-induced antinociception (Zarrindast et al., 1993). Morphine has been shown to release adenosine (Sawynok et al., 1989). Adenosine-dependent mechanisms may be involved in catalepsy (Zarrindast et al., 1997), morphine antinociception (Sawynok et al., 1989; De Lander and Kiel, 1994) and morphine tolerance (Tao et al., 1995). Opioids are known to induce behavioural reinforcing effects (Bilsky et al., 1992) and a major restricting factor in the clinical use of opioids is the fear of drug dependence (Weis et al., 1983). A change in synaptic regulation of dopamine cells in the ventral tegmentum area one week after termination of chronic treatment with morphine has been suggested. A possible long-lasting dopamine–adenosine interaction has been also implicated in dopamine-mediated craving and relapse to drug-seeking behaviours (Bonci and Williams, 1996). Adenosine receptor agonists have shown to decrease naloxone-induced jumping in rats (Dionyssopoulos

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et al., 1992) and in mice (Tucker et al., 1984; Ahlijanian and Takemori, 1985). However, other investigators found no effect for adenosine receptor agonists in this respect in rats (Salem and Hope, 1997) or in mice (Kaplan and Sears, 1996). In the present study, effects of adenosine receptor agonists and antagonists on naloxone-induced jumping and diarrhea in mice were evaluated.

2. Materials and methods

2.1. Animals

Male NMRI mice (23–28 g) were housed in plastic cages in an animal room maintained at 22–25°C on a 12-h dark cycle. Food and water were available at all times except during the experiments. Each animal was used once only and was killed immediately after the experiment.

2.2. Induction of dependence

The mice were rendered dependent on morphine, based on the method we used previously (Zarrindast and Farzin, 1996). Morphine sulfate was injected subcutaneously (s.c.) three times daily at 9:30, 13:30 and 17:30 h on the following dosage schedule. The first three doses were 50, 50 and 75 mg kg^{-1}, respectively. The higher dose of the third daily injection was aimed to minimize any overnight withdrawal. Each of the doses was then increased by 25 mg kg^{-1} day^{-1}. Morphine administration was carried out over a maximum of 3 days for any group of mice. A dose of 50 mg kg^{-1} of morphine sulfate also was injected on the 4th day (2 h before naloxone injection). Hyperactivity and the Straub tail effect were seen after morphine injections. Loss of weight (7–18%) and death (1–2%) were observed with chronic administration of morphine sulfate.

2.3. Naloxone-induced jumping and diarrhea

Groups of mice were tested for the occurrence of jumping after their 10th injection of morphine on day 4. A total of 2 h after the last dose of morphine (50 mg kg^{-1}), abstinence was precipitated by an intraperitoneal (i.p.) injection of naloxone (4 mg kg^{-1}); then the animals were placed individually in a Perspex observation box (20 × 20 cm width, 50 cm height) which was lined with preweighed paper towelling to allow collection of wet and dry faecal matter. The number of jumps was recorded over a 30-min period. The diarrhea induced after naloxone administration was expressed as the weight in grams of faecal material per 100 g body weight in 30 min.

2.4. Drugs

Drugs used were adenosine receptor agonists N^6-cyclohexyladenosine (CHA), $R(-)N^6$-(2-phenylisopropyl)adenosine (R-PIA) and 5′-(*N*-cyclopropyl)-carboxamidoadenosine (CPCA), or adenosine receptor antagonists 8-cyclopentyl-1,3-dipropylxanthine (DPCPX; Sigma, St. Louis, MO, USA), 3,7-dimethyl-1-propargylxanthine (DMPX; Research Biochemical Int., Natick, MA, USA), morphine sulfate (Temad, Iran) and naloxone hydrochloride ampoules (Tolid-Daru, Iran). All drugs were dissolved in 0.9% saline, except DPCPX which was suspended in 1% (W/V) carboxymethylcellulose (CMC) containing 5% (V/V) dimethylsulfoxide (DMSO). The drugs were administered in a volume of 10 ml kg^{-1} body weight i.p., except morphine which was injected s.c. The doses of drugs used were shown to be active in previous studies (Kaplan and Sears, 1996; Zarrindast et al., 1997).

2.5. Data analysis

One-way ANOVA (analysis of variance) followed by Newman–Keuls test or two-way ANOVA followed by Tukey's protected *t*-test was performed. Differences with $P < 0.05$ between experimental groups at each point were considered statistically significant.

3. Results

3.1. Naloxone-induced withdrawal jumping and diarrhea in morphine-dependent mice

Mice were randomly divided into two groups. One group received morphine (as described in Section 2) to

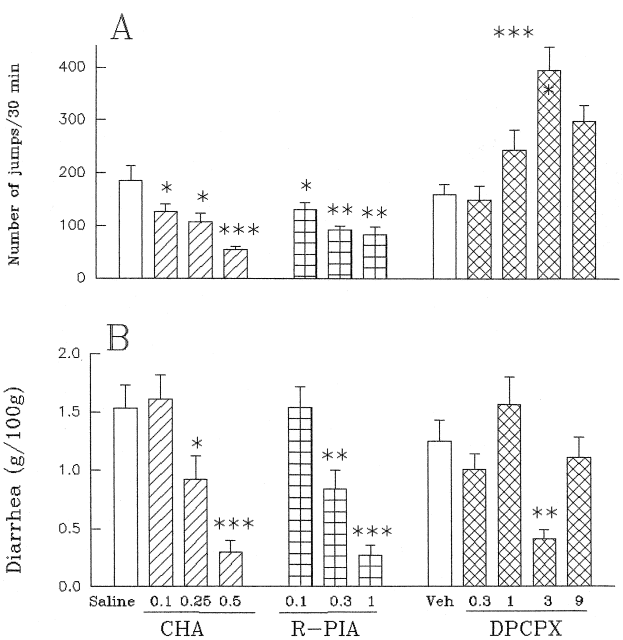

Fig. 1. Effects of adenosine receptor agonists and antagonist on naloxone-induced jumping and diarrhea in morphine-dependent mice. Mice were made dependent as described in Section 2. All the dependent mice received naloxone (4 mg kg^{-1}) to induce jumping and diarrhea. The animals received saline, vehicle (CMC 1% containing 5% DMSO), CHA, R-PIA or DPCPX (0.3–9 mg kg^{-1}) i.p. 1 h before naloxone administration. Each group is comprised of nine mice. Data are means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ $^{***}P < 0.001$, different from the saline or vehicle control group.

induce dependence. The next group received saline (10 ml kg^{-1}) instead of morphine. Naloxone (4 mg kg^{-1}, i.p.) increased the number of jumps in morphine-dependent mice (149 ± 1; $N = 9$) as compared with non-dependent mice (0.2 ± 0.2; $N = 9$, $P < 0.0001$). In the same animals, naloxone administration also increased the amount (grams) of faecal material per 100 g of body weight, in dependent animals (1.7 ± 0.2; $N = 9$) as compared with that for the non-dependent control group (0.6 ± 0.1; $N = 9$, $P < 0.05$). The results showed that naloxone can express the jumping and diarrhea in morphine-dependent mice.

3.2. Effects of adenosine receptor agonists and antagonists on naloxone-induced jumping behaviour and diarrhea in morphine-dependent mice

The adenosine A_1 receptor agonists, CHA (0.1, 0.25 and 0.5 mg kg^{-1}; $F_{3,32} = 9.1$, $P < 0.001$), or R-PIA (0.1, 0.3 and 1 mg kg^{-1}; $F_{3,32} = 6.8$, $P < 0.01$), when administered 60 min before naloxone (4 mg kg^{-1}, i.p.), significantly decreased the jumping response induced by naloxone in morphine-dependent animals. The CHA response seems to be dose-dependent. The diarrhea induced in the animals was also decreased dose dependently by both CHA ($F_{3,32} = 11.1$, $P < 0.0001$) and R-PIA ($F_{3,32} = 14.0$, $P < 0.0001$), respectively. Pretreatment with the adenosine A_1 receptor antagonist, DPCPX (0.3–9 mg kg^{-1}, i.p.), 60 min before naloxone (4 mg kg^{-1}, i.p.), dose relatedly increased the naloxone-induced jumping in morphine-dependent mice ($F_{4,40} = 9.5$, $P < 0.0001$), however, the diarrhea induced by naloxone was decreased with one dose (3 mg kg^{-1}, i.p.) of the drug ($F_{4,40} = 6.3$, $P < 0.001$). The antagonist itself did not induce jumping in morphine-dependent animals (Fig. 1). The data indicate that A_1 receptor activation may reduce jumping and diarrhea induced by naloxone in morphine-dependent mice.

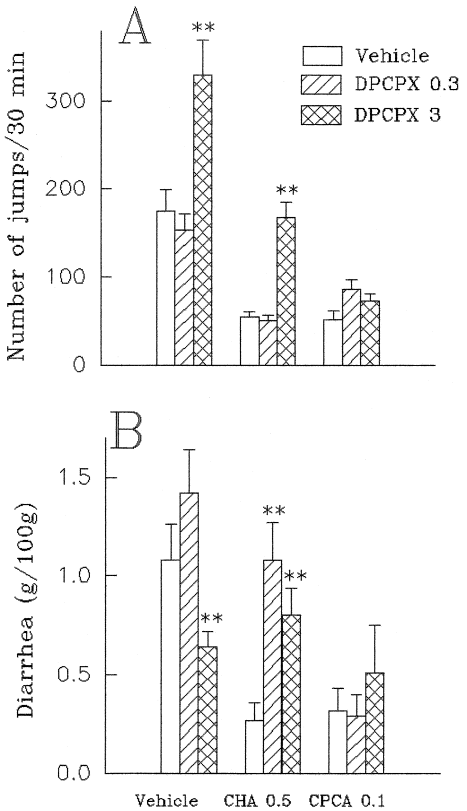

Fig. 3. Effects of adenosine receptor agonists in the presence or absence of the A_1 adenosine receptor antagonist on jumping (A) and diarrhea (B) induced by naloxone in morphine-dependent mice. The animals received vehicle (CMC 1% containing 5% DMSO), DPCPX (i.p.) 15 min before CHA or CPCA. CHA or CPCA was injected (i.p.) 1 h before naloxone administration. Each group is comprised of nine mice. Data are means ± S.E.M. $^{**}P < 0.01$, different from the respective control group.

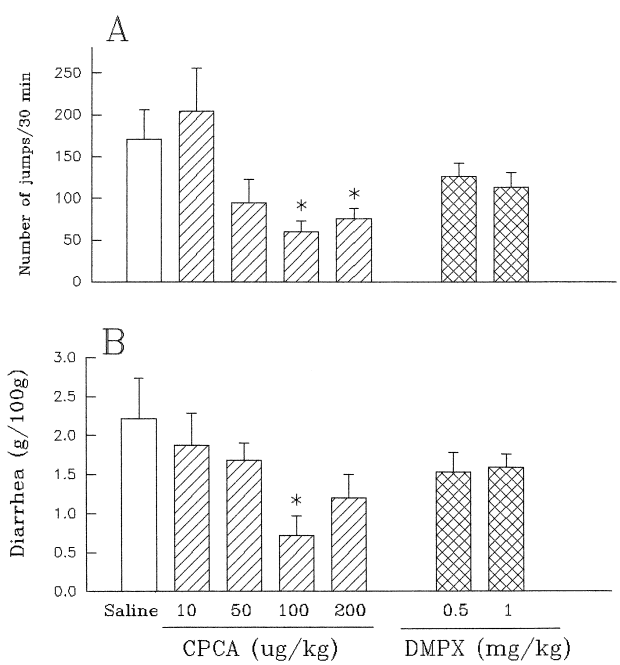

Fig. 2. Effect of A_2 adenosine receptor agonist and antagonist on jumping and diarrhea induced by naloxone. Animals were made dependent as described in Section 2. All the dependent mice received naloxone (4 mg kg^{-1}) to induce jumping and diarrhea. The animals received saline or different doses of CPCA (10–200 μg kg^{-1}) or DMPX (0.5 and 1 mg kg^{-1}) 1 h before naloxone administration. Each group is comprised of nine mice. Data are means ± S.E.M. $^{*}P < 0.05$, different from the saline control group.

With the same procedure, when dependent animals were given the adenosine A_2 receptor agonist, CPCA (10–200 μg kg^{-1}), there was a significant difference between naloxone-induced jumping in CPCA-treated and saline-treated mice ($F_{4,40} = 3.9$, $P < 0.01$). Higher doses of CPCA inhibited the naloxone-induced jumping behaviour. However, only one dose (100 μg kg^{-1}) of the drug reduced the diarrhea ($F_{4,40} = 2.7$, $P < 0.05$). The adenosine A_2 receptor antagonist, DMPX (0.5 and 1 mg kg^{-1}, i.p.), did not alter either jumping ($F_{2,24} = 2.0$, $P > 0.05$) or diarrhea ($F_{2,24} = 0.07$, $P > 0.05$) induced by naloxone (4 mg kg^{-1}, i.p.) in dependent animals (Fig. 2). It seems likely that adenosine A_2 receptor stimulation by higher doses of the agent reduce the naloxone response in the animals.

3.3. Effects of adenosine receptor antagonists on response induced by adenosine receptor agonists

The effects of adenosine receptor agonists in the presence or absence of the adenosine receptor antagonists are shown in Figs. 3 and 4. Two-way ANOVA showed that CHA reduced the naloxone response in morphine-dependent animals. Two-way ANOVA also indicated an interaction between the effects of the adenosine A_1 receptor antagonist, DPCPX (0.3 and 3 mg kg^{-1}, i.p.; $F_{4,72} = 7$, $P < 0.0001$), and the inhibitory response to the adenosine receptor agonists, CHA (0.5 mg kg^{-1}, i.p.) and CPCA (0.1 mg kg^{-1}, i.p.) on jumping induced by naloxone in morphine-dependent animals. Tukey's test showed that DPCPX decreased the inhibitory response to CHA but not that to CPCA on jumping (Fig. 3A). Two-way ANOVA also indicated an interaction between the effects of the adenosine antagonist, DPCPX ($F_{4,72} = 4.4$, $P < 0.01$), with the inhibitory response to the adenosine receptor agonists, CHA and CPCA, on the diarrhea induced by naloxone in morphine-dependent animals. Further analysis showed that DPCPX decreased the inhibitory response to CHA but not that to CPCA (Fig. 3B). Thus, the inhibitory response

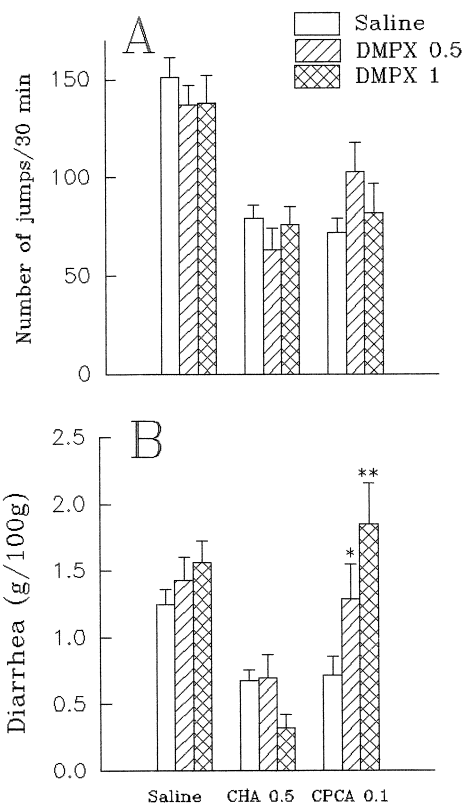

Fig. 4. Effects of adenosine receptor agonists in the presence or absence of the A_2 adenosine receptor antagonist on jumnping (A) and diarrhea (B) induced by naloxone in morphine-dependent mice. The animals received saline or DMPX (i.p.) 15 min before CHA or CPCA. CHA or CPCA was injected (i.p.) 1 h before naloxone administration. Each group is comprised of nine mice. Data are means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$, different from the respective control group.

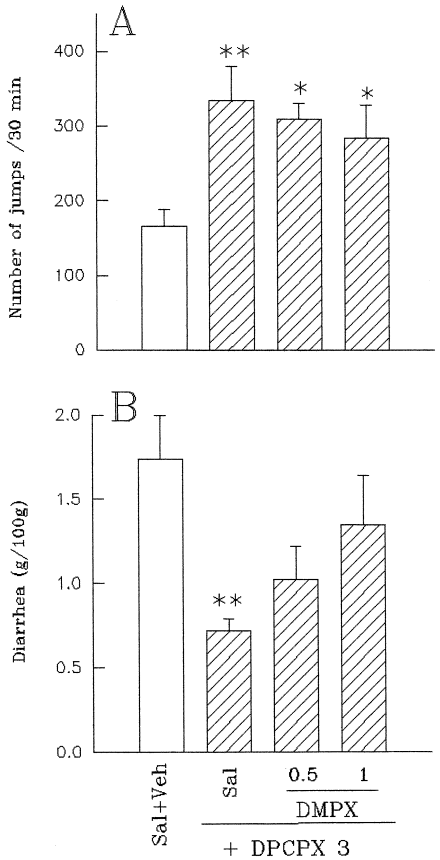

Fig. 5. Effects of A_1 adenosine receptor antagonist, DPCPX in the presence or absence of the A_2 adenosine receptor antagonist, DMPX on jumnping (A) and diarrhea (B) induced by naloxone in morphine-dependent mice. The animals received vehicle, DPCPX (3 mg kg^{-1}, i.p.) or DPCPX plus DMPX (0.5 and 1 mg kg^{-1}, i.p.). DPCPX or DMPX were injected (i.p.) 1 h before naloxone administration. Each group had nine mice. Data are means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$, different from the respective control group.

induced by adenosine A_1 receptor activation could be decreased by blockade of the receptors.

The adenosine A_2 receptor antagonist, DMPX (0.5 and 1 mg kg^{-1}, i.p.), did not alter the effect of CHA or CPCA on jumping ($F_{4,72} = 1.0$, $P > 0.05$; Fig. 4A), however, the antagonist reduced the inhibitory response to CPCA but not to CHA ($F_{4,72} = 4.5$, $P < 0.01$) on diarrhea (Fig. 4B). Thus, adenosine A_2 receptor blockade reduced the inhibition of naloxone-induced diarrhea through stimulation of the adenosine A_2 receptors.

The effects of the combination of adenosine A_1 and A_2 receptor antagonists are shown in Fig. 5. There was a significant difference between the jumping (ANOVA, $F_{3,32} = 4.6$, $P < 0.01$) and the diarrhea ($F_{3,32} = 3.9$, $P < 0.05$) induced in animals treated with saline, DPCPX, or the combination of DPCPX with DMPX. Further analysis showed that the increase in naloxone-induced jumping by DPCPX could not be altered by DMPX, however, DMPX could block the inhibitory response to DPCPX on naloxone-induced diarrhea.

4. Discussion

In the present study, CHA and R-PIA, which are adenosine receptor agonists (Jacobson et al., 1992), decreased naloxone-induced jumping. Similar results have been reported by others (Tucker et al., 1984; Ahlijanian and Takemori, 1985; Dionyssopoulos et al., 1992). In agreement with others (Tucker et al., 1984), we did not observe sedation with low doses (0.1 and 0.25 mg kg^{-1}) of the adenosine agents. Thus, the data may suggest that an adenosine-dependent mechanism(s) is involved in morphine dependence. However, there are reports that adenosine agonists do not influence naloxone-induced jumping (Kaplan and Sears, 1996; Salem and Hope, 1997). The adenosine A_1 receptors are widely distributed in the brain (Fredholm et al., 1994; Olah and Stiles, 1995). Since the adenosine receptor agonists, CHA and R-PIA have more affinity for adenosine A_1 receptors (Daly, 1982; Fredholm et al., 1994), and the receptor A_1 antagonist, DPCPX (Jacobson et al., 1992; Fredholm et al., 1994), decreased the inhibitory response to CHA, adenosine A_1 receptors may be involved in the response. However, the adenosine A_1 receptor antagonist by itself also increased naloxone-induced jumping, which is consistence with some reports (Salem and Hope, 1997) but not with others (Kaplan and Sears, 1996).

In the present study, the higher doses of the adenosine A_2 receptor agonist, CPCA (Daly, 1982), also reduced naloxone-induced jumping and the effect was not antagonized by the adenosine A_1 or A_2 receptor antagonists. This effect of CPCA may not be mediated through adenosine receptor mechanism, since the drug doses were high, no adenosine receptor antagonists reduced the response and since other authors (Dionyssopoulos et al., 1992; Kaplan and Sears, 1996; Salem and Hope, 1997) reported no effect for adenosine A_2 receptors in this respect.

Adenosine A_1 and A_2 receptors have been shown to be present in the gastrointestinal tract (Murthy et al., 1995). The adenosine A_1 receptor agonists, CHA and R-PIA, and also a higher dose of an adenosine A_2 receptor agonist, CPCA, reduced the naloxone-induced diarrhea. The response elicited by the adenosine A_1 and A_2 receptor agonists was reduced by the adenosine A_1 receptor antagonist, DPCPX (Jacobson et al., 1992), and the adenosine A_2 receptor antagonist, DPMX (Seale et al., 1988), respectively. Thus, stimulation of both the adenosine A_1 and A_2 receptors may be involved in the inhibition of diarrhea by the agents. The adenosine A_2 receptors are divided into two subtypes, A_{2a} and A_{2b} sites, and the adenosine A_{2b} receptors have been shown to be located in the gastric tissues (Fredholm et al., 1994; Olah and Stiles, 1995). Thus, one may speculate that a peripheral mechanism is involved in the response induced by CPCA. However, there is a report indicating that the spinal cord may be a site of opioid effects on gastrointestinal transit in the mouse (Porreca and Burks, 1983). Presynaptic adenosine A_1 receptor blockade may release adenosine, which in turn may activate postsynaptic adenosine receptors involved in the inhibition of diarrhea induced by naloxone. This hypothesis gains support from the by fact that combination of adenosine A_2 receptor antagonist, DMPX with the adenosine A_1 receptor antagonist, DPCPX, is able to decrease this later effect induced by DPCPX. It should be mentioned that the results obtained with the adenosine receptor antagonists by some investigators (Kaplan and Sears, 1996) indicating that DPCPX has no effect on diarrhea and that DMPX increases the diarrhea induced by naloxone, are not in agreement with our findings.

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