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Attenuating effect of adenosine receptor agonists on the development of behavioral sensitization induced by sporadic treatment with morphine

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ABSTRACT

The aim of the study is to investigate the effect of adenosine receptor agonists on the development of morphine-induced sensitization to the locomotor activity of mice. Selective A1 (N^6-cyclopentyladenosine – CPA) and A2A (2-p-(2-carboxyethyl) phenethylamino-5'-*N*-ethylcarboxamidoadenosine hydrochloride – CGS 21680) adenosine receptor agonists or non-selective A1/A2A (5'-*N*-ethylcarboxamidoadenosine – NECA) adenosine agonists as representatives of adenosinergic drugs have been used in the experiment. Behavioral sensitization has been obtained by sporadic treatment with morphine (10.0 mg/kg, i.p.). We have shown that adenosine receptor agonists co-administered with morphine significantly attenuates increase in the locomotor activity of mice evoked by challenge dose of morphine. These effects have been observed after stimulation of the selective A1 or A2A and non-selective A1/A2A adenosine receptors, namely both receptors were involved in morphine-induced sensitization. Thus, we have demonstrated that adenosine agonists are able to inhibit behavioral sensitization induced by sporadic applications of morphine.

1. Introduction

Behavioral sensitization is defined as the progressive enhancement of locomotor effect of opioids or psychostimulants following their repeated and intermittent administration. As literature data have shown the sensitization plays an important role in the etiology and maintenance of drug-seeking behavior as well as in relapse to drug use, even after long-term abstinence period (Robinson and Berridge, 1993, 2000; Stewart and Badiani, 1993). Behavioral sensitization is the subject of numerous investigations which major purpose is the recognition of mechanisms underlying phenomenon of relapse to drug use and providing new strategies for the treatment of drug addiction. Currently, cocaine and amphetamine sensitization is the most recognized (Li et al., 2005; Thomas et al., 2008; Vanderschuren and Kalivas, 2000) although numerous studies also confirm the development of sensitization after sporadic treatment with nicotine (Biała, 2003; Fredrickson et al., 2003), ethanol (Kotlińska et al., 2006; Pastor and Aragon, 2006) diazepam (Listos et al., 2008a) or morphine (Grecksch et al., 2006; Lévesque et al., 2008; Kotlińska and Bocheński, 2007). The expression of sensitization to the locomotor effects of opiates is known to be at least partially regulated by dopamine (Le Moal and Simon, 1991; Vanderschuren and Kalivas, 2000). Morphine produces the biochemical and behavioral effects via stimulation of the μ opioid receptor in the central nervous system and directly inhibits γ-aminobutyric acid (GABA) neurons resulting in an increase in mesolimbic dopamine neurotransmission (Vanderschuren and Kalivas, 2000; Kalivas and Stewart, 1991). The neurotransmitters, such as GABA (Bartoletti et al., 2007; Zarrindast et al., 2008), nitric oxide (Manzanedo et al., 2009) or dopamine (Lan et al., 2009) are involved in the effect of morphine sensitization.

Adenosine, a potent inhibitory neuromodulator in the central nervous system, acts via four adenosine receptor subtypes: A1, A2A, A2B and A3 from A1 and A2A which are the most recognized. A1 receptors are highly expressed in different brain areas, such as cortex, cerebellum, hippocampus, and dorsal horn of spinal cord. Distribution of A2A receptors is more limited, mainly in the striato-pallidal GABAergic neurons and olfactory bulb. In other brain areas they are expressed in lower levels (Ferré et al., 1997). It has been repeatedly shown that adenosine is involved in the effects of morphine and opioid system. It is known that extracellular levels of adenosine is increased after exposure to morphine or the other abused drugs (Baldo et al., 1999) and adenosine may be responsible for the modification of addictive behavior in animals. In biochemical studies an increase in number of A1 adenosine receptors in brain and a decrease of A2A receptors in striatum have been demonstrated in morphine dependent rats (Ahlijanian and Takemori, 1986; De Montis et al., 1992; Kaplan et al., 1994). In morphine tolerant mice the up-regulation of striatal and hypothalamic adenosine transporter-binding sites has also been shown (Kaplan and Leite-Morris, 1997). Furthermore, a close functional interaction in vitro between adenosine A1, A2A receptors and morphine withdrawal was also described

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by Capasso and Gallo (2009). The involvement of adenosine ligands in the effect of chronic opiate treatment was also demonstrated in behavioral experiments. For example, adenosine agonists were able to reduce opiate withdrawal signs in mice (Kaplan and Sears, 1996) as well as the development of morphine sensitization was inhibited by adenosine receptor antagonists in the C57BL/6 mouse (Weisberg and Kaplan, 1999). Previously we also indicated that stimulation of adenosine A2A receptors attenuated the development of hypersensitivity to an acute dose of morphine during morphine withdrawal (Listos et al., 2008b). The other studies showed that motivational properties induced by morphine were reduced in A2A receptor knockout mice in conditioned place-preference paradigm (Castañé et al., 2008) and the self-administration of morphine was decreased in these animals (Brown et al., 2009). Therefore, in the present experiments, we undertook to study the effect of adenosine receptor agonists on the development of morphine-induced sensitization to the locomotor activity in mice. Locomotor activity is thought to be the main behavior that can be used to detect behavioral sensitization in rodents. First we assessed the effect of adenosine ligands on locomotor activity of mice. For this reason both selective A1 (CPA), A2A (CGS 21680) and non-selective A1/A2A (NECA) adenosine receptor agonists were used as representatives of adenosinergic drugs. Then we studied if sporadic treatment with morphine developed behavioral sensitization, manifested as increase in locomotor activity in mice. Finally, we evaluated if adenosine receptor agonists co-administered with morphine affected the morphine-induced sensitization in mice. All these experiments were undertaken to study the adenosinergic mechanisms involved in behavioral sensitizations.

2. Materials and methods

2.1. Animals

The experiments were carried out on male albino Swiss mice (20–30 g). The animals were kept 8–10 per cage at room temperature of 22 1 °C, on natural day–night cycle (spring). Standard food (Murigran pellets, Bacutil, Motycz) and tap water were freely available. All the experiments were made between 9 a.m. and 2 p.m. After 1 week of adaptation and handling, the animals were divided into groups (10–14 animals/group) and prepared for the tests.

The study was performed according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and the European Community Council Directive for Care and Use of Laboratory Animals and were approved by local ethics committee (The Medical University of Lublin Committee on the Use and Care of Animals).

2.2. Drugs

The following drugs were used in the experiments: morphine hydrochloride (Polfa, Kutno, Poland) and adenosine receptor ligands: N^6-cyclopentyladenosine (CPA) – the selective adenosine A_1 receptor agonist; 2-p-(2-carboxyethyl)phenethylamino-5'-*N*-ethylcarboxamidoadenosine hydrochloride (CGS 21680) – the selective adenosine A_{2A} receptor agonist; 5'-*N*-ethylcarboxamidoadenosine (NECA) – the non-selective adenosine A_1/A_2 receptor agonist; (all from Sigma-Aldrich, St. Louis, USA).

CPA, CGS 21680 and morphine were dissolved in saline, NECA was dissolved in minimal volume of ethanol (5–7 drops) and then it was diluted in saline.

All drugs were given intraperitoneally (i.p.) in a volume of 10.0 ml/kg.

The following doses of drugs were used in the experiments: 10.0 mg/kg of morphine (i.p.); 0.05, 0.1 and 0.2 mg/kg of CPA (i.p.); 0.025, 0.05 and 0.1 mg/kg of CGS 21680 (i.p.) and 0.0005, 0.001 and 0.002 mg/kg of NECA (i.p.).

The control group animals received the same volume of saline at the respective time before the test.

2.3. Apparatus

The locomotor activity in mice was measured in round actometer cages (32 cm in diameter, Multiserv, Lublin, Poland), which were kept in a sound-attenuated experimental room. The cages were equipped with one row of infrared light-sensitive photocells located 1 cm above the floor. Locomotor activity was measured for the total period of 60 min.

2.4. Procedures

In the first step of the study the acute effect of adenosine receptor agonists on locomotor activity of mice was studied. At 15 min after injection of adenosine agonist (CPA, CGS 21680 or NECA) mice were placed into actometer for 60 min. Simultaneously, we studied the effect of adenosine agonists with an acute dose of morphine. Animals received morphine 15 min after injection of adenosine agonist and then they were placed into actometer immediately for the same period.

In the second, morphine-induced behavioral sensitization in mice was developed. Sensitization procedure was based on the method described by Kuribara (1997) with modification described by Kotlińska and Bocheński (2007). Mice received five intraperitoneal (i.p.) injections of morphine at a dose of 10 mg/kg every 3 days (on the 1st, 4th, 7th, 10th, 13th day). Seven days after the last treatment (on the 20th day) mice were treated with a challenge dose of morphine (10 mg/kg, i.p.) or saline (control group). To assess the development of behavioral sensitization, mice were immediately placed into actometer cages to record the locomotor activity for the period of 60 min.

Next, the effect of adenosine receptor agonists (CPA, CGS 21680 or NECA) on morphine-induced sensitization was explored. Adenosine agonists were administered 15 min before the morphine injection on the 1st, 4th, 7th, 10th and 13th day of the experiment, but not on the 20th day.

2.5. Statistical analysis

The obtained data, presented in the figures as mean ± S.E.M, were statistically calculated using one-way (for effect of adenosine ligands) or repeated measures two-way (for assessment of sensitization development) analysis of variance (ANOVA). Post hoc comparisons were carried out by means of Tukey test. A probability (P) value of 0.05 or less was considered as statistically significant. Each group of animals consisted of 10–14 mice.

3. Results

All adenosine receptor agonists were used in the experiments at ineffective doses, namely, when they were given alone they had no influence on spontaneous locomotor activity of animals (Fig. 1). Similarly, simultaneous injection of each adenosine agent with an acute, ineffective dose of morphine (10.0 mg/kg) also did not change the activity of mice (Fig. 1).

An intermittent treatment with morphine (10.0 mg/kg) gradually increased the locomotor activity of mice. Two-way ANOVA showed significant effect of drug ($F_{1,12} = 58.83$, $P<0.0001$), day ($F_{5,12} = 9.607$, $P = 0.0007$) but not interaction ($F_{5,12} = 0.6445$, $P = 0.6709$). Post hoc comparison confirmed that the most significant effect ($P<0.001$) was observed on the 20th day of the experiment, when challenge dose of morphine (10.0 mg/kg) was injected after 7-day cessation period (Fig. 2). Five intermittent injections of each adenosine agonist with morphine (on the 1st, 4th, 7th, 10th, and 13th day of the experiment)

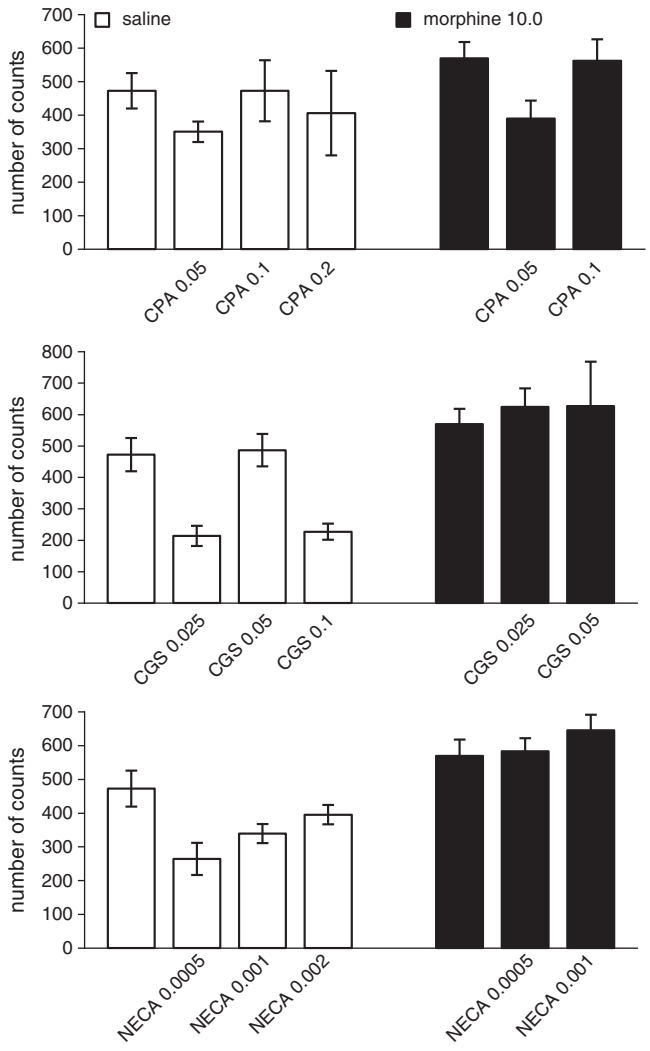

Fig. 1. Effects of acute doses of different adenosine agonists (CPA: 0.05, 0.1 and 0.2 mg/kg, i.p.; CGS 21680: 0.025, 0.05 and 0.1 mg/kg, i.p.; NECA: 0.0005, 0.001, and 0.002 mg/kg, i.p.), morphine (10 mg/kg, i.p.) and combination of adenosine agonists/morphine on spontaneous locomotor activity of mice. Morphine-induced locomotor activity was recorded immediately after drug injection while adenosine agonists were injected 15 min before the measurement. Results are expressed as mean ± S.E.M. (n = 10–14 mice/group). One-way ANOVA did not show any significant changes in locomotor activity of mice.

significantly reduced the effect of challenge dose of morphine on the 20th day in mice: CPA ($F_{2,31}$ = 17.43, P<0.0001), CGS 21680 ($F_{2,31}$ = 9.133, P = 0.0008) or NECA ($F_{2,31}$ = 18.22, P<0.0001). Post hoc comparisons showed that locomotor activity of animals was significantly reduced after challenge dose of morphine in mice received both doses of all adenosine agonists: CPA (0.05 and 0.1 mg/kg) – P<0.01 and P<0.001, respectively; CGS (0.025 and 0.05 mg/kg) – P<0.01 and P<0.1, respectively; and NECA (0.0005 and 0.001 mg/kg) – P<0.001 and P<0.01, respectively (Fig. 3).

4. Discussion

The study consisting of three-step experiments has tested the involvement of adenosine receptor agonists on development of morphine sensitization to the locomotor effect in mice. The obtained results have demonstrated that all used ligands had no influence on locomotor activity of mice. In line with these results two lowest doses of each adenosine agonist were chosen to the next part of the study. Next we indicated that intermittent treatment with morphine gradually induced an increase in locomotor activity. The most intensified effect was produced by the challenge dose of morphine

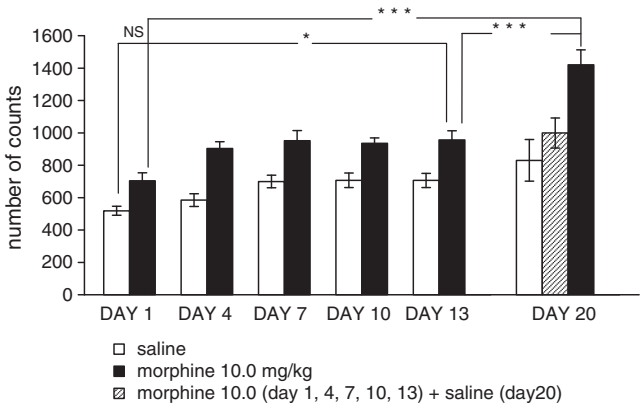

Fig. 2. Effect of challenge dose of morphine on sporadic treatment with ineffective dose of morphine (10.0 mg/kg, i.p.) of mice as the confirmation of the development of morphine-induced behavioral sensitization in mice. Five morphine injections were administered every 3 days (on the 1st, 4th, 7th, 10th, 13th day) and challenge dose of morphine were administered after 7-day drug-free period. After each morphine injection, mice were immediately placed in actometer. Results are expressed as mean ± S.E.M. (n = 10–14 mice/group). Two-way ANOVA showed significant changes in locomotor activity. ***P<0.001, *P<0.05, ^{NS}P>0.05 (Tukey test).

on the 20th day of the study, demonstrating that behavioral sensitization had been developed. Behavioral sensitization is an effect of sporadic treatment with abused drugs in animals, which manifests mainly as an increase in locomotor activity. This marked increase in locomotor activity reflects drug-seeking behavior which leads directly to drug taking. According to Robinson and Berridge hypothesis (Robinson and Berridge, 2000), sensitization refers to typical behavior of addicted patients. It is well known that the development of behavioral sensitization depends on the circumstances surrounding drug administration, which are responsible for the appearance of appetitive behavior. Therefore, in the experiments we used homogenous procedures in the whole study: the experiments were conducted in routine procedure, the animals were always put in the same cages and the experiments were conducted at the same time. Thus, the significant increase in locomotor activity after challenge dose of morphine confirmed the development of behavioral sensitization which is closely associated with drug-seeking behavior in mice.

The major finding of the study, however, is the indication that concomitant injections of adenosine receptor agonists with morphine

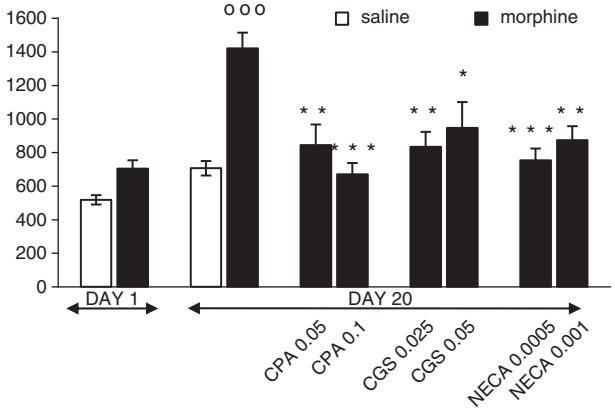

Fig. 3. The effect of challenge dose of morphine (10.0 mg/kg, i.p.) in mice sporadically treated with morphine and adenosine agonists (CPA: 0.05 and 0.1 mg/kg, i.p.; CGS 21680: 0.025 and 0.05 mg/kg, i.p.; NECA: 0.0005 and 0.001 mg/kg, i.p.) Adenosine agonists were administered 15 min before morphine injections on the 1st, 4th, 7th, 10th, 13th day of the experiment. On the 20th day mice received only the challenge dose of morphine. The results are expressed as mean ± S.E.M. (n = 10–14 mice/group). Two-way ANOVA showed significant changes in locomotor activity. ***P<0.001, **P<0.01, *P<0.05 vs. morphine on 20th day; ^{ooo}P<0.001 vs. morphine on 1st day (Tukey test).

significantly attenuated the effect of the challenge dose of morphine, namely, adenosine receptor agonists were able to inhibit behavioral sensitization and appetitive behavior. These effects were observed after selective A1 or A2A and non-selective A1/A2A stimulation of adenosine receptors demonstrating the involvement of both receptors in sensitization. It should be highlighted that on the 20th day of the study, the animals received only the challenge dose of morphine. Thus, we have shown that five injections of adenosine agonists with morphine produce persistent changes in central nervous system and, in fact, adenosine agonists via A1 and A2A receptors have protective effect on the development of behavioral sensitization. Our result has confirmed the data of the other authors. Sahraei et al. (1999) demonstrated that CGS 21680, but not NECA, increased morphine self-administration when drugs were injected on the test day, and both CGS 21680 and NECA decreased the morphine self-administration when they were administered analogically to our experiment during the training session. Thus, our results have strongly supported the significance of adenosine agonists as an inhibiting factor on behavioral sensitization induced by morphine.

The role of adenosine A2A receptors in rewarding effect of drugs of abuse is not fully understood. According to our results the other authors have shown that CGS 21680, the adenosine A2A receptor agonist, was also able to inhibit the development of cocaine and methamphetamine sensitization to locomotor activity (Shimazoe et al., 2000; Filip et al., 2006) and CGS 21680 and NECA inhibited the initiation of cocaine self-administration in rats (Knapp et al., 2001). The acquisition of diazepam sensitization to withdrawal signs was also reduced by CGS 21680 (Listos et al., 2008a). On the other hand, the results of experiments with adenosine antagonists do not always confirm our conclusions because a blockade of these receptors produces non-homogenous effects in experiments. For example, the non-selective A1 and A2A antagonist (CGS 15943) reinstated cocaine-seeking behavior and maintained self-administration in baboons (Weerts and Griffiths, 2003) and caffeine, the well-known antagonist of A1 and A2A receptors, prevented the extinction of cocaine-seeking behavior in mice (Kuzmin et al., 1999). While, the other authors demonstrated that blockade of adenosine A2A receptors eliminated heroin-seeking behavior in rats (Yao et al., 2006). These data are difficult to discussion, and we suppose, it depends on different factors: kind of drug of abuse and adenosine ligands – their doses and selectivity for presynaptic versus postsynaptic adenosine receptors.

On the other hand, the results of the study in A2A receptor knockout mice provide more clear conclusions. An acute response after morphine administration in mice lacking A2A receptors was similar to this in wild type. However, both the rewarding and aversive effects associated with morphine abstinence were completely abolished in mice lacking the A2A receptors (Castañé et al., 2008). Brown et al. (2009) also showed the decrease morphine self-administration in mice lacking A2A receptor. In that study there were no observed differences in both expression and development of morphine sensitization to the locomotor activity in two genotypes. These results could be explained by reduction in dopamine–adenosine interaction in A2A knockout mice and, consequently, decrease in dopamine release in mesolimbic system and decrease in rewarding effect of morphine in these mice.

The involvement of adenosine A1 receptor in drug-seeking behavior, however, is not so evident. We have shown the significant inhibition of morphine-induced sensitization by CPA in our study, while in the other study, the development of methamphetamine-induced sensitization has not been changed by cyclohexiloadenosine, the other adenosine A1 receptor agonist (Shimazoe et al., 2000). We presume that such a difference could be associated with the discrepancy between morphine and methamphetamine mechanisms of action. For example, in the effect of CPA in morphine-induced sensitization the GABAergic mechanisms could be joined. This hypothesis however needs further studies.

The significance of adenosine receptor agonists in addiction is also suppressed by experiments in which the involvement of adenosine ligands in tolerance to abused drugs was investigated. Tolerance, as a reduction in pharmacological activity of psychoactive drugs which appears after chronic treatment with them, is an important factor of the state of dependence. In our previous study we have shown that mainly adenosine A2A receptors play a significant role in attenuation of development of diazepam tolerance in mice (Listos et al., 2010). On the other hand, the other authors demonstrated the involvement of adenosine A1 receptors in ethanol-induced tolerance (Batista et al., 2005). Thus, the ability of adenosine ligands to modulate the state of dependence supports their importance in exploration of different aspects of addiction.

The molecular mechanism of action of morphine and behavioral sensitization is currently recognized. It is known that morphine, by stimulation of μ and δ, but not κ receptors, leads to inhibition of GABAergic interneurons, thereby disinhibiting mesolimbic dopaminergic neurons and increasing dopamine release in mesolimbic system. (Vanderschuren and Kalivas, 2000; Kalivas and Stewart, 1991). It is also known that sporadic treatment with morphine induces biochemical changes in dopamine pathways manifested as oversensitivity to ineffective dose of the drug. This oversensitivity is associated with the increase in dopamine release and is expressed as the increase in locomotor activity in animals. Moreover, from among dopaminergic pathways, especially projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) (Le Moal and Simon, 1991), are thought to play the key role in behavioral sensitization. Other studies have shown that VTA is the most important structure in the development of morphine sensitization, because microinjection of morphine into VTA, but not into NAcc, results in development of sensitization (Joyce and Iversen, 1979; Vezina et al., 1987; Vezina and Stewart, 1989). On the other hand, there is a novel hypothesis of development of sensitization which postulates that oligomerization of dopamine receptors may underlie this phenomenon. The repeated stimulation of dopamine monomeric receptors by abused drugs, like morphine, may cause to form the heteromeric receptor complexes in the brain and may alter the functional properties of receptors, like ligand-binding affinity or signaling (Franco et al., 2000; Tsai and Hong, 2003; Canals et al., 2003; Fuxe et al., 2006; Hillion et al., 2002). These receptor adaptations may underlie the oversensitivity developed after sporadic treatment with abused drugs, and we hypothesized these adaptations might be responsible for the intensified effect of the challenge dose of morphine in our study.

The mechanism by which adenosine agonists alter behavioral response to morphine following their repeated administration is probably mediated through modulation of dopaminergic neurotransmission. Close interactions between dopaminergic and adenosinergic receptors have been demonstrated repeatedly. Adenosine A1 receptors are widely distributed in the central nervous system (Williams and Braunwalder, 1986) and antagonistic interactions between A1–D1 receptors have been precisely described (Ferré, 1997; Ferré et al., 1994, 1996). Adenosine A2A receptors are mainly located in reach dopamine and D2 receptor areas of the central nervous system, like striatum, nucleus accumbens or olfactory tubercle (Jarvis and Williams, 1989; Schiffmann et al., 1991) and their antagonizing effect to D2 receptors has also been indicated in numerous studies (Ferré, 1997; Ferré et al., 1991, 1996). Thus, we presume that in our study stimulation of A1 or A2A receptors antagonizes D1 or D2 receptors, respectively, and protects them to formulate the biochemical changes induced by sporadic treatment with morphine.

The acute effect of CGS 21680 and NECA on locomotor activity of mice is surprising. Generally, it has been repeatedly shown that adenosine receptor agonist dose-dependently decreased locomotor activity of animals (Barraco et al., 1994; Durcan and Morgan, 1989). However, in these experiments the higher doses of CGS 21680 and

NECA were used. In our present experiments we aspired to using ineffective doses of drugs. As shown Fig. 1, the lowest dose of CGS 21680 and NECA tend to decrease in locomotor activity of mice. We suppose that some interactions between A2A and A1 receptors in hippocampus may be expressed after treatment with such low doses of these drugs.

In conclusion, behavioral sensitization is a major characteristic of drug addiction and could be used to study the effects of dependent drugs. It is expressed as an increase in locomotor activity after sporadic treatment with morphine or other psychostimulants. The findings, which reveal the morphine-induced sensitization in mice, show analogies with the phenomenon observed among addicted patients. In humans, drug-seeking behavior is strongly manifested even after long-term cessation period, especially when the circumstances are related to drug use. We have demonstrated that sporadic treatment with morphine induced the significant increase in locomotor activity of mice and this effect was significantly inhibited by adenosine agonists. It is reasonable to conclude that adenosine agonists may play an important role in drug-induced mechanisms underlying drug-seeking behavior and relapse to use. Since adenosine receptor agonists show some beneficial effects in the phenomenon of sensitization, withdrawal signs or tolerance, this class of compounds could offer interesting approach to the pharmacotherapy of addiction.

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