Pharmacological Reports
2008, 60, 679–685
ISSN 1734-1140

Involvement of adenosine receptor agonists on the development of hypersensitivity to acute dose of morphine during morphine withdrawal period

Joanna Listos, Sylwia Talarek, Sylwia Fidecka

Department of Pharmacology and Pharmacodynamic, Medical University of Lublin, Staszica 4, PL 20-081 Lublin, Poland

Correspondence: Joanna Listos, e-mail: alistos@op.pl

Abstract:
In the present study, the involvement of the selective adenosine A_1 (CPA) and A_{2A} (CGS 21680) and non-selective adenosine A_1/A_{2A} (NECA) receptor agonists on the development of hypersensitivity to acute morphine injection given during opiate withdrawal was investigated. Intraperitoneal (*ip*) injections of morphine at increasing doses (10, 20, 30, 40, 50 mg/kg) for 6 consecutive days produced a state of dependence. On the 6th day, in the morning, animals were injected with the last dose of morphine (50 mg/kg, *ip*). Each day, 20 min before each injection of morphine, adenosine receptor agonists were also administered. Seven days after cessation of the morphine treatment, on the 13th day of the experiment, all animals were challenged with a dose of morphine (10 mg/kg, *ip*). A clear increase in locomotor activity was observed, indicating that hypersensitivity had developed. Our study has demonstrated the presence of an attenuating effect of adenosinergic drugs, such as CGS 21680 and NECA, but not CPA, on the development of hypersensitivity. The results indicate that stimulation of the adenosine A_{2A} receptor plays some role in modulating the neuroadaptive changes appearing during chronic opioid treatment and that adenosine A_{2A} receptor agonists may serve as useful drugs in relapse protection. Our investigations focused on adenosine A_{2A} agonists as possible vehicles for pharmacotherapy for morphine addiction.

Key words:
adenosine receptor agonists, morphine withdrawal signs, hypersensitivity

Abbreviations: CGS 21680 – 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine hydrochloride, CPA – N^6-cyclopentyladenosine, NECA – 5'-N-ethylcarboxamidoadenosine

Introduction

Morphine and other opioids clinically used as analgesics are also illegally used as recreational drugs and result in addiction. Therefore, the effects of repeated exposures to these compounds are important topics for studies on drug-dependent mechanisms. It is known that repeated treatment with these drugs intensifies their ability to exert effects on the central nervous system, leading to the development of sensitization, an important factor in the development of dependence [12]. It is thought that an increase in sensitivity to opioids is observed even after long periods of abstinence and may be responsible for relapses to drug-seeking behavior [23]. The mechanisms underlying opioid dependence have been extensively

studied in experimental animals, and numerous findings have shown that dopamine plays a key role in that process [26]. The ventral tegmental area, nucleus accumbens, and prefrontal cortex seem to be the most important brain areas involved in opioid dependence [15, 27]. In addition to the dopaminergic pathways, the involvement of neurotransmitter and neuromodulator systems in opioid-dependent mechanisms has been recently documented. The glutamatergic [14, 21] and γ-aminobutyric acid (GABAergic) systems [7] are the most engaged in opioid dependence, although the role of other modulators, such as nitric oxide [28] or adenosine, cannot be ruled out.

Endogenous adenosine, a potent inhibitory neuromodulator in the central nervous system, is known to affect the state of dependence. For example, opioid [9], ethanol [10], or benzodiazepine [16] withdrawal signs have been attenuated by treatment with adenosine receptor agonists. Additionally, Knapp et al. [11] have shown that 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine hydrochloride (CGS 21680) and 5'-N-ethylcarboxamidoadenosine (NECA) inhibit the initiation of cocaine self-administration. In our previous experiments, we have demonstrated that CGS 21680 and NECA inhibited the development of sensitization to diazepam withdrawal signs [17], and adenosine receptor antagonists intensified diazepam and temazepam withdrawal signs [16]. Thus, the adenosinergic system is well-recognized as an important modulator of dependence, but relatively less is known about behavioral consequences of the effects of adenosine ligands on the development of hypersensitivity to acute morphine doses, injected during morphine withdrawal periods. The present study is undertaken to investigate the role of the selective adenosine A_1 (CPA) and A_{2A} (CGS 21680) and non-selective A_1/A_{2A} (NECA) receptor agonists on the development of hypersensitivity to acute morphine injections given during opiate withdrawal. Repeated exposure to morphine and other abused drugs induces characteristic effects on locomotor activity in experimental animals; therefore, in the present study, we have chosen locomotor activity as the parameter to measure the development of hypersensitivity. The obtained results are discussed in the context of behavioral changes induced by chronic morphine treatment leading to addiction, especially in connection with adenosine receptors in the central nervous system.

Materials and Methods

Animals

The experiments were carried out on male albino Swiss mice (20–30 g). The animals were kept 8–10 per cage at a room temperature of 22 ± 1°C on natural day-night cycles (spring). Standard food (Murigran pellets, Bacutil, Motycz) and tap water were freely available. All the experiments were performed between 9 a.m. and 2 p.m.

The study was performed in accordance with the opinion of the Local Ethics Committee.

Drugs

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

Morphine and all the adenosine receptor ligands were dissolved in saline, and they were given intraperitoneally (*ip*).

The following doses of the adenosine agonists were used in the study: CPA (0.025 and 0.05 mg/kg, *ip*), CGS 21680 (0.05 and 0.1 mg/kg, *ip*), and NECA (0.001 and 0.002 mg/kg, *ip*). All drugs were administered in a volume of 10 ml/kg.

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

Apparatus

The locomotor activity of mice was measured in round actometer cages (32 cm in diameter), which were kept in a sound-attenuated experimental room. Two photocell beams located across the long axis measured the animals' movements.

Procedure

Physical dependence on morphine in mice was produced by twice daily injections of morphine at increasing doses (10, 20, 30, 40, 50 mg/kg, *ip*) for 5 consecutive days. In the morning of day 6, the ani-

mals were injected with the last dose of morphine (50 mg/kg, *ip*). Each day, 20 min before each injection of morphine, the adenosine receptor agonists or saline were also administered. Seven days later, on the 13th day of the study, all animals were challenged with a dose of morphine (10 mg/kg, *ip*).

The locomotor activity of the mice was evaluated for a period 1 h, following administration of morphine, both on the 1st and 13th day of the experimental period. Each group of animals consisted of 10 mice.

Statistical analysis

The data are expressed as locomotion counts (the means ± SEM). To evaluate the hypersensitivity to morphine injection, the response to morphine on day 13 was compared with the acute drug response to the first injection (on 1st day) in the same animals, or with the response to the challenge morphine injection (on 13th day) in adenosine ligands-treated mice. Data were analyzed by the analysis of variance (two-way ANOVA). The *post-hoc* comparison of means was carried out using the Tukey test. A probability (p) value of 0.05 or less was considered statistically significant.

Results

To induce the hypersensitivity to a challenge dose of morphine given during morphine withdrawal, morphine was administered at increasing doses for six consecutive days. Seven days after cessation of morphine treatment, on the 13th day of the study, the administration of the challenge dose of morphine (10 mg/kg, *ip*) significantly intensified (Fig. 2, $p < 0.01$; Fig. 3 and 4, $p < 0.001$) the locomotor activity of mice compared to the activity in response to acute morphine injection (10 mg/kg, *ip*) given on the 1st day of the experiment, demonstrating the development of morphine hypersensitivity.

CPA (0.025 and 0.05 mg/kg, *ip*), the selective adenosine A_1 receptor agonist, given 20 min before each injection of morphine (excluding day 13 of the experiment) had no effect on the development of hypersensitivity (Fig. 2). In contrast, significant inhibition of the development of morphine hypersensitivity was obtained with the higher dose of CGS 21680 (0.1 mg/kg, *ip*, $p < 0.001$), the selective adenosine A_{2A} receptor agonist, and both doses of NECA (0.001 mg/kg, $p < 0.001$ and 0.002 mg/kg, $p < 0.01$, *ip*), the non-selective adenosine A_1/A_{2A} receptor agonist (Fig. 3 and 4).

The acute doses of all adenosine receptor agonists: CPA, CGS 21680, and NECA given alone did not alter the locomotor activity of mice (Fig. 1), and the adenosine ligands, given together with an acute dose

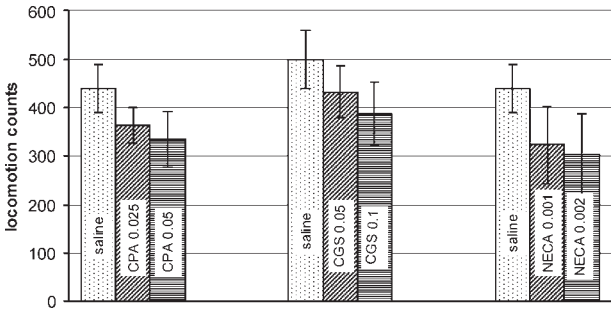

Fig. 1. Effect of adenosine receptor agonists on locomotor activity of mice. Animals received adenosine agonists: CPA (0.025 and 0.05 mg/kg, *ip*), CGS 21680 (0.05 and 0.1 mg/kg, *ip*) and NECA (0.001 and 0.002 mg/kg, *ip*) 20 min before the beginning of the test. Locomotor activity was recorded for 60 min. Each point shows the mean ± SEM of locomotion counts for 10 mice. Two-way analysis did not show a significant effect

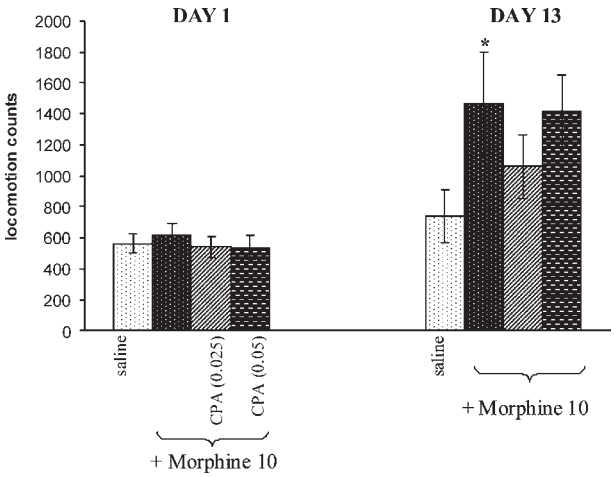

Fig. 2. Effect of CPA (0.025 and 0.05 mg/kg, *ip*) on the development of hypersensitivity to an acute dose of morphine (10 mg/kg, *ip*) given on the 7th day of the morphine withdrawal period. Morphine was injected at increasing doses for six consecutive days. 20 min before each dose of morphine, the animals received CPA. On day 13, the animals were challenged with morphine. The locomotor activity was measured for 60 min. Each point shows the mean ± SEM of locomotion counts for 10 mice. * $p < 0.05$ *vs.* respective group on the 1st day (Tukey test)

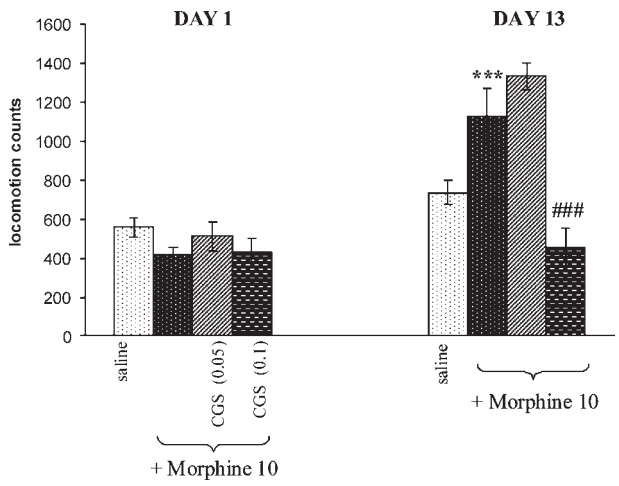

Fig. 3. Effect of CGS 21680 (0.05 and 0.1 mg/kg, *ip*) on the development of hypersensitivity to an acute dose of morphine (10 mg/kg, *ip*) given on the 7th day of the morphine withdrawal period. Morphine was injected at increasing doses for six consecutive days. 20 min before each dose of morphine, the animals received CGS. On day 13 the animals were challenged with morphine. The locomotor activity was measured for 60 min. Each point shows the mean ± SEM of locomotion counts for 10 mice. *** $p < 0.001$ *vs.* respective group on the 1st day, ### $p < 0.001$ *vs.* group of mice challenged with morphine on 13th day, which has no previous history of CGS 21680 (Tukey test)

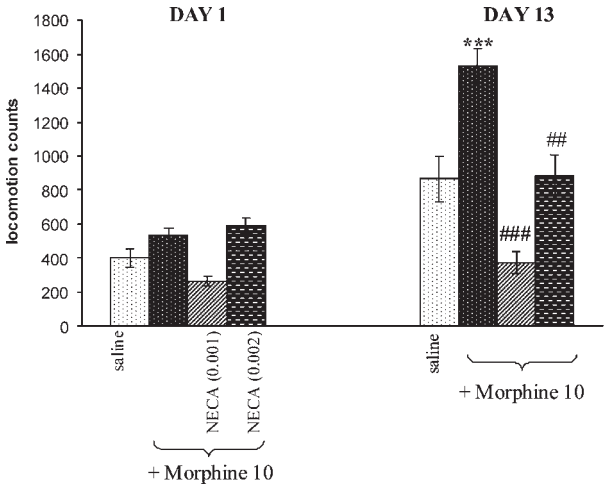

Fig. 4. Effect of NECA (0.001 and 0.002 mg/kg, *ip*) on the development of hypersensitivity to an acute dose of morphine (10 mg/kg, *ip*) given on the 7th day of the morphine withdrawal period. Morphine was injected at increasing doses for six consecutive days. 20 min before each dose of morphine, the animals received NECA. On day 13 the animals were challenged with morphine. The locomotor activity was measured for 60 min. Each point shows the mean ± SEM of locomotion counts for 10 mice. *** $p < 0.001$ *vs.* respective group on the 1st day, ## $p < 0.01$, ### $p < 0.001$ *vs.* group of mice challenged with morphine on 13th day, which has no previous history of NECA (Tukey test)

of morphine (10 mg/kg, *ip*), also did not change the locomotor activity of mice (Fig. 2–4).

Discussion

In the present study, we have examined the influence of selective and non-selective adenosine receptor agonists on the development of hypersensitivity to an acute morphine injection given during opiate withdrawal. In the first step of our experiment, the animals received morphine for six consecutive days. In the second step, the morphine administration was discontinued. During that period, some changes in behavior, such as anxiogenic effects or diarrhea, appeared. These changes were not recorded. In the third step of our study, on the 13th day of the experiment, the challenge dose of morphine was injected. At that time, we observed changes in behavior, a clear increase in locomotor activity, indicating that hypersensitivity to the acute morphine injection given during opiate withdrawal had developed. We have found that the development of hypersensitivity was significantly attenuated by adenosine receptor agonists, such as CGS 21680 and NECA, but not CPA. Indeed, in mice simultaneously treated with morphine and the higher dose of CGS 21680 or either dose of NECA for several days, we observed clear inhibition of hypersensitivity to the acute morphine injection, reflected by significant reductions in locomotion counts in mice. However, CPA, the selective adenosine A_1 receptor agonist, did not produce such effects. All adenosine agonists given alone did not affect the locomotor activity of mice (Fig. 1). Our findings support the hypothesis that stimulation of adenosine A_{2A} receptor plays some modulatory role in the neuroadaptive changes appearing during chronic opioid treatment.

Interestingly, in our study, NECA, the non-selective adenosine A_1/A_{2A} receptor agonist, given at the lower dose of 0.001 mg/kg, produced larger effects on the development of hypersensitivity than the higher dose of that drug. We suggest that the dose-independent effect of that non-selective agonist is presumably associated with the interaction between A_1 and A_{2A} receptors in the central nervous system [22, 24]. A recent report has shown that under basal conditions, adenosine stimulates mainly A_1 receptors, while under conditions of greater adenosine release, A_{2A} re-

ceptors are activated. A_{2A} receptors are then able to block A_1-mediated function, inducing glutamate release [4]. In our study, it is likely that the higher dose of NECA strongly stimulated A_{2A} receptors, inducing the blockade of A_1 receptors and the attenuation of locomotor activity of mice.

The rewarding effect of morphine and other opioids is related to stimulation of opioid receptors by these drugs and to a decrease in GABAergic pathways in dopaminergic neurons, resulting in an increase in dopamine concentrations in the ventral tegmental area [3]. Repeated morphine exposure produces adaptive changes in opioid receptors and neurons, leading to dysregulation of endogenous opioid, as well as non-opioid, pathways in the central nervous system. For example, in biochemical experiments, it has been shown that turnover of monoamines, such as dopamine and serotonin, is decreased, but turnover of noradrenaline is increased during opioid withdrawal, and acute morphine injection during that period accelerated the turnover of all three monoamines [2]. Acquas and Di Chiara [1] have demonstrated that withdrawal from morphine produces a marked reduction of extracellular dopamine concentrations in the mesolimbic system of rats, mainly on days 3, 5, and 7 of the withdrawal period, and that challenge with morphine during this period results in stimulation of dopamine output. The neuroadaptive changes described above are responsible for the appearance of altered behavior during opiate withdrawal, such as dysphoria or the enormous desire for the drug. The renewed exposure to the drug during the withdrawal period induces more intense effects of morphine, commonly leading to a relapse in drug use. The relapse is an important factor for identification of the neurobiological mechanisms related to the long-lasting hyperresponsiveness of mesencephalic dopaminergic pathways in the brain, which develops after chronic exposure to drugs of abuse. Consistent with these findings, in our experiments, the repeated exposure to increasing doses of morphine has produced a state of dependence in which the activity of neuronal transmissions, mainly dopaminergic pathways, has been altered. In the present experiments, the challenge dose of morphine given on day 7 of the withdrawal period produced clear hypersensitivity to the drug, and we suggest that this hypersensitivity may result from above mentioned hyperresponsiveness of dopaminergic pathways, studied by Acquas and Di Chiara [1]. The most important finding of our experiments is that the selective and non-selective adenosine receptor agonists, CGS 21680 and NECA, but not CPA, co-administered with morphine for six consecutive days, have prevented the development of hypersensitivity. Thus, we have shown that adenosine A_{2A} receptor agonists may be useful as drugs targeting relapse prevention.

At present, the mechanism by which adenosine receptor agonists modify the opioid dependence is uncertain. We suppose that the well-described interaction between adenosine and dopamine receptors in the brain appears to play a crucial role in the observed effects. The numerous biochemical and behavioral experiments have demonstrated that adenosine and dopamine play the opposite role in central nervous system. For example, adenosine agonists inhibited the locomotor activity induced by dopamine receptor agonists [8]. Ferre et al. [5] demonstrated that CGS 21680 significantly decreased the dopamine affinity for dopamine D_2 receptors and that CGS 21680 was ineffective in altering D_1 receptor affinity. This A_{2A}-D_2 interaction was specific, without adenosine A_1 or dopamine D_1 receptor involvement, giving an important, biochemical explanation for the A_{2A}-D_2 interaction postulated from behavioral data. Based on these data, it appears possible that the inhibition of hypersensitivity development by CGS 21680 and NECA, as observed in our study, is indirectly related to the long-term inhibitory effect on morphine-induced release of dopamine in brain. The blockage of dopamine D_2 receptors co-localized with A_{2A} receptors on striatopallidal GABAergic neurons [6] seems to play the most important role in the attenuation of the development of neuroadaptive changes in neuronal pathways in brain resulting from chronic morphine treatment.

On the other hand, morphine and other opioids are important regulators of the hypothalamic-pituitary-adrenal axis, exerting a stimulatory effect on corticotropin-releasing factor (CRF). CRF, acting on CRF_1 and CRF_2 receptors, plays an important role in activation of the sympathetic system, and is able to modulate behavioral and physiological responses to stress (for ref. see [19]). Several pieces of data have shown that anxiogenic and aversive symptoms of withdrawal from many abused drugs, such as cocaine, ethanol, tetrahydrocannabinol, and morphine contribute to an increase in CRF release [13] and that the activity of the hypothalamic-pituitary-adrenal axis is intensified during the withdrawal period [20]. Other findings have reported that CRF plays an important role in

reinstatement of drug-seeking behavior induced by stressors [25], demonstrating the significant function of CRF in the mechanism of dependence. Although the exact role of CRF in dependence is not well-recognized, Lu et al. [18] have shown that the CRF_1 receptor is more involved in morphine withdrawal signs and in relapse to morphine dependence than the CRF_2 receptor. Thus, taking into consideration all the data, the role of the hypothalamic-pituitary-adrenal axis in modulating effect of opioid dependence, as observed in our study, cannot be excluded. Moreover, considering the CRF-dependent mechanism of opioid action, it is difficult to explain connections with A_{2A} receptors, which are mainly involved in the development of hypersensitivity to the acute morphine injection given during opiate withdrawal. There are no data in the literature describing co-interaction between adenosine and CRF. Thus, we can only suppose that the modulating effect of adenosine and CRF in the hippocampus, *via* A_{2A} and CRF_1 receptors, respectively, may be responsible for that process.

In summary, the results of the present study suggest that adenosine A_{2A} receptor agonists have slow the appearance of adaptive changes in the central nervous system developing during repeated exposure to morphine. Treatment with CGS 21680 and NECA strongly attenuated the hypersensitivity to a challenge dose of morphine, the effect of which is often responsible for the relapse in drug use. It is thus reasonable to conclude that adenosine agonists may play an important role in opioid-induced neural mechanisms underlying the development of dependence. Thus, our investigations strongly focused on adenosine A_{2A} agonists as interesting vehicles for pharmacotherapy for morphine addiction.

References:

1. Acquas E, Di Chiara G: Depression of mesolimbic dopamine transmission and sensitization to morphine during opiate abstinence. J Neurochem, 1992, 58, 1620–1625.
2. Ahtee L, Attila LM, Carlson KR, Haikala H: Changes in brain monoamine metabolism during withdrawal from chronic oral self-administration of morphine and in response to a morphine challenge in the withdrawn state. J Pharmacol Exp Ther, 1989, 249, 303–310.
3. Bailey CP, Connor M: Opioids: cellular mechanisms of tolerance and physical dependence. Curr Opin Pharmacol, 2005, 5, 60–68.
4. Ciruela F, Casadó V, Rodrigues RJ, Luján R, Burgueño J, Canals M, Borycz J et al.: Presynaptic control of striatal glutamatergic neurotransmission by adenosine A_1-A_{2A} receptor heteromers. J Neurosci, 2006, 26, 2080–2087.
5. Ferre S, von Euler G, Johansson B, Fredholm BB, Fuxe K: Stimulation of high-affinity adenosine A_2 receptors decreases the affinity of dopamine D_2 receptors in rat striatal membranes. Proc Natl Acad Sci, 1991, 88, 7238–7241.
6. Fredholm BB, Ijzerman AP, Jacobson KA, Klotz KN, Linden J: International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. Pharmacol Rev, 2001, 53, 527–552.
7. Hack SP, Vaughan CW, Christie MJ: Modulation of GABA release during morphine withdrawal in midbrain neurons in vitro. Neuropharmacology, 2003, 45, 575–584.
8. Heffner TG, Wiley JN, Williams AE, Bruns RF, Coughenour LL, Downs DA: Comparison of the behavioral effects of adenosine agonists and dopamine antagonists in mice. Psychopharmacology, 1989, 98, 31–37.
9. Kaplan GB, Bharmal NH, Leite-Morris KA, Adams WR: Role of Adenosine A_1 and A_{2A} receptors in the alcohol withdrawal syndrom. Alcohol, 1999, 19, 157–162.
10. Kaplan GB, Leite-Morris KA, Sears MT: Alterations of adenosine A_1 receptors in morphine dependence. Brain Res, 1994, 657, 347–350.
11. Knapp CM, Foye MM, Cottam N, Ciraulo DA, Kornetsky C: Adenosine agonists CGS 21680 and NECA inhibit the initiation of cocaine self administration. Pharmacol Biochem Behav, 2001, 68, 797–803.
12. Koob GF: Neuroadaptive mechanisms of addiction: studies on the extended amygdala. Eur Neuropsychopharmacol, 2003, 13, 442–452.
13. Koob GF, Heinrichs SC: A role for corticotropin releasing factor and urocortin in behavioral responses to stressors. Brain Res, 1999, 848, 141–152.
14. Kotlińska J, Bocheński M: Comparison of the effects of mGluR1 and mGluR5 antagonists on the expression of behavioral sensitization to the locomotor effect of morphine and the morphine withdrawal jumping in mice. Eur J Pharmacol, 2007, 558, 113–118.
15. Le Moal M, Simon H: Mesocorticolimbic dopaminergic network: functional and regulatory roles. Physiol Rev, 1991, 71, 155–234.
16. Listos J, Malec D, Fidecka S: Adenosine receptor antagonists intensify the benzodiazepine withdrawal signs in mice. Pharmacol Rep, 2006, 58, 643–651.
17. Listos J, Talarek S, Fidecka S: Adenosine receptor agonists attenuate the development of diazepam withdrawal-induced sensitization in mice. Eur J Pharmacol, 2008, 588, 72–77.
18. Lu L, Liu D, Ceng X, Ma L: Differential roles of corticotropin-releasing factor receptor subtypes 1 and 2 in opiate withdrawal and in relapse to opiate dependence. Eur J Neurosci, 2000, 12, 4398–4404.
19. Macey DJ, Koob GF, Markou A: CRF and urocortin decreased brain stimulation reward in the rat: reversal by a CRF receptor antagonist. Brain Res, 2000, 866, 82–91.
20. Milanés MV, Laorden ML, Chapleur-Château M, Burlet A: Alterations in corticotropin-releasing factor

and vasopressin content in rat brain during morphine withdrawal: correlation with hypothalamic noradrenergic activity and pituitary-adrenal response. J Pharmacol Exp Ther, 1998, 285, 700–706.
21. Noda Y, Nabeshima T: Opiate physical dependence and N-methyl-D-aspartate receptors. Eur J Pharmacol, 2004, 500, 121–128.
22. Ribeiro JA: Adenosine A_{2A} receptor interactions with receptors for other neurotransmitters and neuromodulators. Eur J Pharmacol, 1999, 375, 101–113.
23. Robinson TE, Berridge KC: The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction, 2000, 95, 91–117.
24. Schiffmann SN, Fisone G, Moresco R, Cunha RA, Ferré S: Adenosine A_{2A} receptors and basal ganglia physiology. Prog Neurobiol, 2007, 83, 277–292.
25. Shaham Y, Erb S, Leung S, Buczek Y, Stewart J: CP-154,526, a selective, non-peptide antagonist of the corticotropin-releasing factor1 receptor attenuates stress-induced relapse to drug seeking in cocaine- and heroin-trained rats. Psychopharmacology, 1998, 137, 184–190.
26. Spanagel R, Weiss F: The dopamine hypothesis of reward: past and current status. Trends Neurosci, 1999, 22, 521–527.
27. Vanderschuren LJ, Kalivas PW: Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology, 2000, 151, 99–120.
28. Zarrindast MR, Gholami A, Sahraei H, Haeri-Rohani A: Role of nitric oxide in the acquisition and expression of apomorphine- or morphine-induced locomotor sensitization. Eur J Pharmacol, 2003, 482, 205–213.

Received:
February 6, 2008; in revised form: August 27, 2008.