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Adenosine receptor agonists attenuate the development of diazepam withdrawal-induced sensitization in mice

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ABSTRACT

In the present study, the effects of adenosine agonists on the development of sensitization to withdrawal signs precipitated after sporadic treatment with diazepam, in mice, were investigated. To obtain the sensitization, the animals were divided into groups: continuously and sporadically treated with diazepam (15.0 mg/kg, s.c.). The adenosine receptor agonists (CPA, CGS 21680 and NECA) were administered in sporadically diazepam treated mice during two diazepam-free periods. Concomitant administration of pentetrazole (55.0 mg/kg, s.c.) with flumazenil (5.0 mg/kg, i.p.) after the last injection of diazepam or vehicle, induced the withdrawal signs, such as clonic seizures, tonic convulsion and death episodes. The major finding of our experiments is attenuation of withdrawal signs in sensitized mice, inducing by all adenosine agonists. Only higher dose of CPA produced significantly decreased the number of withdrawal incidents, while both used doses of CGS 21680 and NECA produced more clear effects. These results support the hypothesis that adenosinergic system is involved in the mechanisms of sensitization to the benzodiazepine withdrawal signs, and adenosine A_{2A} receptors play more important role in that process.

1. Introduction

Sensitization is the enhanced response to the stimuli related to the repeated exposure to the psychoactive substances. The numerous findings have demonstrated that mesolimbic and mesocortical dopamine system play the most important role in the mechanism of sensitization (Di Chiara et al., 2004, Koob 1992).

At present, the sensitization is the most recognized in the case of cocaine and amphetamine, although the numerous studies also confirm the development of sensitization to effects of morphine (Grecksch et al., 2006; Kotlińska et al., 2005), nicotine (Biała 2003; Biała and Węglińska, 2004a, b; Fredrickson et al., 2003) and ethanol (Kotlińska et al., 2006; Pastor and Aragon, 2006). However, relatively less is known about the repeated exposure to benzodiazepines, the most effective anxiolytic and sedative drugs. Admittedly, several findings (for Ref. see Hutchinson et al., 1996) support the hypothesis that chronic exposure to benzodiazepines induces the development of tolerance to some behavioral effects and physical dependence. However, the sensitization to the effects of benzodiazepines is poorly described. Ward and Stephens (1998) have experimentally shown that severity of the benzodiazepine withdrawal signs increases following several episodes of withdrawal in mice, demonstrating the possibility of the development the sensitization to benzodiazepine withdrawal signs, but more exact aspects of benzodiazepine sensitization have yet not been studied.

It is generally accepted, that the GABAergic system is mainly involved in the effects of benzodiazepines. Initially, based on the resemblance of benzodiazepine and adenosine activity, such as antianxiety, sedative or anticonvulsant effects, it was suggested that the adenosinergic system was involved in the mechanism of benzodiazepine drugs (Arvidson et al., 1982; Hawkins et al., 1988; Phillis et al., 1980; Phillis et al., 1981). At present, however, it is well known, that mechanism of benzodiazepines is mainly related to $GABA_A$ receptors, and adenosine, as the most important neuromodulator in the central nervous system (Fredholm et al., 2001; Ribeiro, 1999) is able to modulate the activity of benzodiazepine compounds.

Adenosine affects the synaptic transmission via four adenosine receptor subtypes: A_1, A_{2A}, A_{2B} and A_3. The close interconnections between the adenosinergic system and different neuronal pathways, particularly dopaminergic, glutamatergic and GABAergic systems (Ferre et al., 1997; Fredholm et al., 2001; Ribeiro, 1999) are responsible for modulating properties of adenosine. Therefore, adenosinergic system was able to affect, as it was experimentally demonstrated, the development of tolerance, sensitization and physical dependence to a variety of psychoactive drugs such as opioids, cocaine or ethanol (Batista et al., 2005; El Yacoubi et al., 2001; Fiorillo and Williams, 2000; Kaplan et al., 1999; Kaplan et al., 1994; Knapp et al., 2001; Weiseberg and Kaplan 1999). In these studies the role of both adenosine A_1 and A_{2A} receptors was indicated. In our previous experiments (Listos et al., 2005. Listos et al., 2006) we investigated the involvement of adenosinergic system in the mechanisms of benzodiazepine dependence. Adenosine receptor agonists were able to attenuate diazepam and temazepam

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withdrawal signs, while adenosine receptor antagonists intensified the observed effects. We also demonstrated that adenosine A_1 receptor played more important role in these effects. The obtained results, however, are extremely difficult to discuss and to comparison because we have not found the behavioral studies related to benzodiazepine dependence and adenosinergic agents.

Taking into account modulating properties of adenosine in benzodiazepine activity and poorly characterized behavioral sensitization to these drugs, the present experiments were undertaken to investigate the sensitization to withdrawal signs precipitated after sporadic treatment with diazepam in mice. We first examined if repeated episodes of diazepam withdrawal escalated the following episodes of withdrawal. From among diazepam withdrawal signs, such as increase in muscle tone, body weight loss or anxiety, in the present study the increase in seizure activity of mice was chosen, as the clear and easy to the measuring symptom, to evaluate the intensity of diazepam withdrawal. Additionally, in accordance with the findings suggesting that adenosinergic system may be an important factor in several aspects of addiction, in a second step of our study, the influence of adenosine receptor agonists on the mechanism of sensitization to diazepam withdrawal signs was investigated. We have chosen three adenosine ligands, such as 5′-*N*-ethylcarboxamidoadenosine (NECA), the non-selective adenosine A_1 and A_{2A} receptor agonist (Bruns et al., 1986), N^6-cyclopentyladenosine (CPA), a compound with high affinity to A_1 receptor (Klotz et al., 1989) or 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamidoadenosine hydrochloride (CGS 21680), which mainly stimulates A_{2A} receptors (Jarvis et al., 1989). The use of the selective and non-selective adenosine receptor agonists made possible the assessment the role of particular adenosine receptors in the observed effects. The results were discussed in the context of functional association of adenosinergic system with neuroadaptive changes in brain structure and function caused by repeated treatment with diazepam. We believe that our study extends the knowledge of benzodiazepine dependence mechanisms.

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.

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

2.2. Drugs

The following drugs were used: diazepam (Relanium, amp., Polfa-Poland), flumazenil (Hoffman-La Roche, Swiss), pentetrazole (Sigma-Aldrich, USA), 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, USA).

The CPA and CGS 21680 were dissolved in saline. NECA was dissolved in minimal volume of ethanol and then, it was diluted in saline. Diazepam, as the solution for injection, was diluted in saline. Pentetrazole was dissolved in saline. Flumazenil was dissolved in the minimal volume of dimethylsulfoxide (DMSO), and diluted in saline. The adenosine analogs and flumazenil were administered intraperitoneally (i.p.), and other drugs were injected subcutaneously (s.c.).

Basing on the literature data (Baldo et al., 1999; Justinova et al., 2003; Knapp et al., 2001; Salem and Hope, 1997) and no published our experiments minimal effective doses of the drugs have been chosen. In the experiments the following doses of drugs have been used: diazepam (15.0 mg/kg, s.c.) pentetrazole (55.0 mg/kg, s.c.), flumazenil (5.0 mg/kg, i.p.), CPA (0.025 and 0.05 mg/kg, i.p.), CGS 21680 (0.1 and 0.2 mg/kg, i.p.), NECA (0.005 and 0.01 mg/kg, i.p.).

All the drugs were administered in a volume of 10.0 ml/kg.

2.3. Procedure

The daily and chronic (21 days) administration of diazepam (15.0 mg/kg, s.c.) produced benzodiazepine dependence in mice (accordingly to Ward and Stephens, 1998). In order to show the sensitization to benzodiazepine withdrawal signs we adapted the protocol of Ward and Stephens (1998). According to that, the animals were divided into groups: the animals continuously (for 21 days)

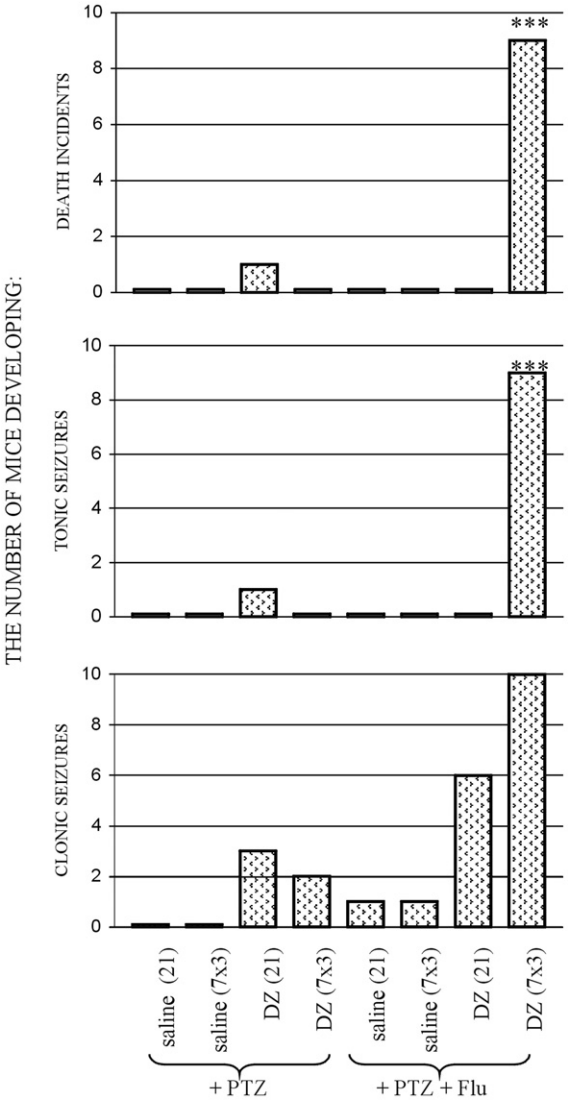

Fig. 1. Effects of subthreshold dose of pentetrazole (PTZ: 55.0 mg/kg, s.c.) alone, and pentetrazole with flumazenil (Flu: 5.0 mg/kg, i.p.) on chronically diazepam (DZ: 15.0 mg/kg, s.c.) treated mice. To obtain the development of sensitization to diazepam withdrawal signs the animals were divided into two groups: continuously treated with diazepam (DZ 21) and sporadically treated with diazepam (DZ 7 × 3). Pentetrazole and flumazenil were injected 48 h after the last diazepam injection. Data represent the number of mice responding with withdrawal signs. $n = 10$, $^{***}P < 0.001$ vs continuous diazepam treated mice (DZ 21) in which the withdrawal signs were induced by concomitant injections with pentetrazole and flumazenil (the Fisher exact test).

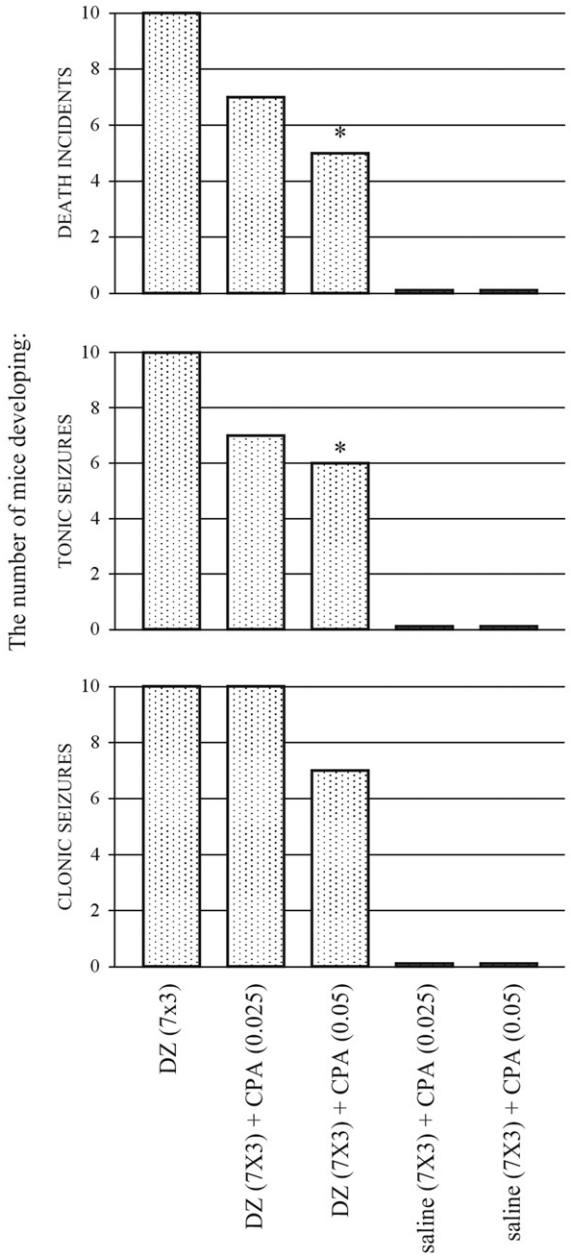

Fig. 2. Effect of CPA (0.025 and 0.05 mg/kg, i.p.) on the development of sensitization to diazepam withdrawal signs. CPA was injected in mice during diazepam-free periods (three, daily injections of CPA in each of that period). The withdrawal signs were induced 48 h after the cessation of diazepam treatment by simultaneous injection of pentetrazole and flumazenil. Data represent the number of mice responding with withdrawal signs. $n=10$, * $P<0.05$ vs sporadically diazepam treated mice (DZ 7 × 3) (the Fisher exact test).

treated with diazepam (*continuous treatment*) and the animals receiving diazepam during three 7-day periods interspersed with 3-day diazepam-free period (*sporadic treatment*) in which the animals were treated vehicle injections. The adenosine receptor agonists (CPA, CGS 21680 and NECA) were administrated in sporadic diazepam treated mice during the diazepam-free periods (three, daily injections of adenosine analogs in each of the periods).

In all animals, the intensity of benzodiazepine withdrawal signs, observed as the increase in seizure activity, was assessed 48 h after the last injection of diazepam or vehicle. During that time, the concomitant administration of subthreshold dose of pentetrazole (55.0 mg/kg, s.c.) with flumazenil (5.0 mg/kg, i.p.) induced immediately the withdrawal signs in mice. Then, the animals were placed in glass cylinders, and they were observed for 1 h. The number of mice developing the clonic seizures, tonic convulsion and death episodes was recorded in that period.

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

2.4. Statistical analysis

The obtained data were analyzed statistically using non-parametric analysis of variance, the Fisher exact test. All the comparisons were performed on drug treated mice and appropriate control group. A probability (P) value of 0.05 or less was considered as statistically significant. Each group of animals was consisted of 10 mice.

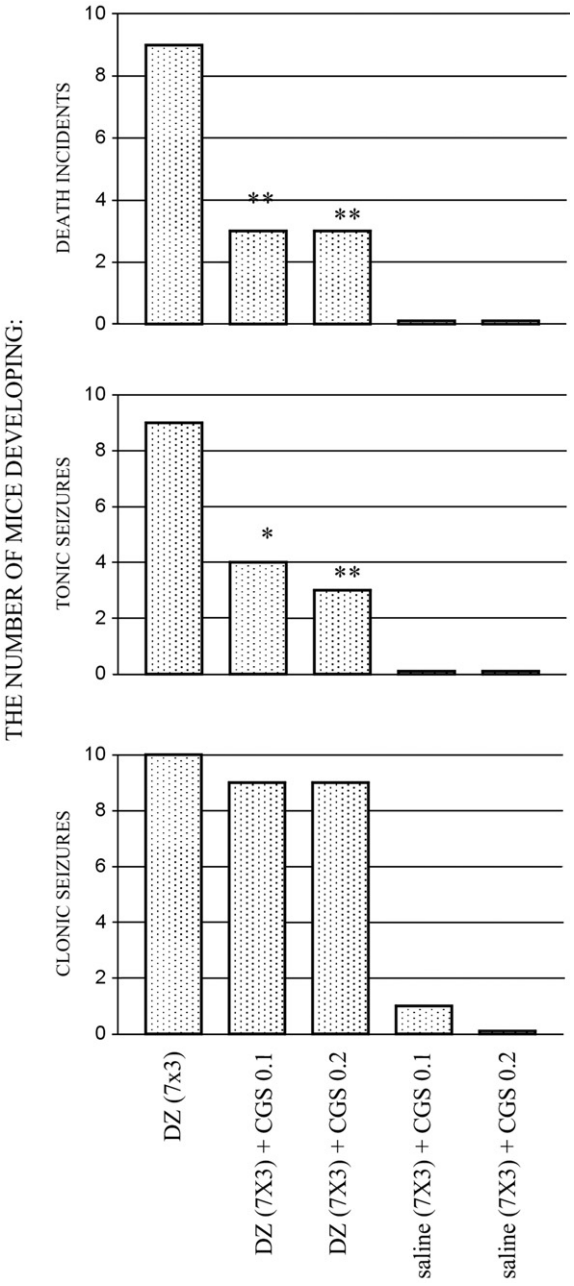

Fig. 3. Effect of CGS 21680 (0.1 and 0.2 mg/kg, i.p.) on the development of sensitization to diazepam withdrawal signs. CGS 21680 was injected in mice during diazepam-free periods (three, daily injections of CGS 21680 in each of that period). The withdrawal signs were induced 48 h after the cessation of diazepam treatment by simultaneous injection of pentetrazole and flumazenil. Data represent the number of mice responding with withdrawal signs. $n=10$, *$P<0.05$, **$P<0.01$ vs sporadically diazepam treated mice (DZ 7 × 3) (the Fisher exact test).

3. Results

As shown in Fig. 1, the most intensify withdrawal incidents (clonic seizures, tonic convulsions and death episodes) were induced by simultaneous injections with subthreshold dose of pentetrazole (55.0 mg/kg, s.c.) and flumazenil (5.0 mg/kg, i.p.) in diazepam-chronically treated mice, especially in those, receiving diazepam sporadically: most of these animals responded with clonic seizures, tonic convulsions and death. In the case of tonic convulsions and death episode the observed effects were significantly intensified in comparison with those, observed in continuously diazepam treatment mice ($P<0.001$).

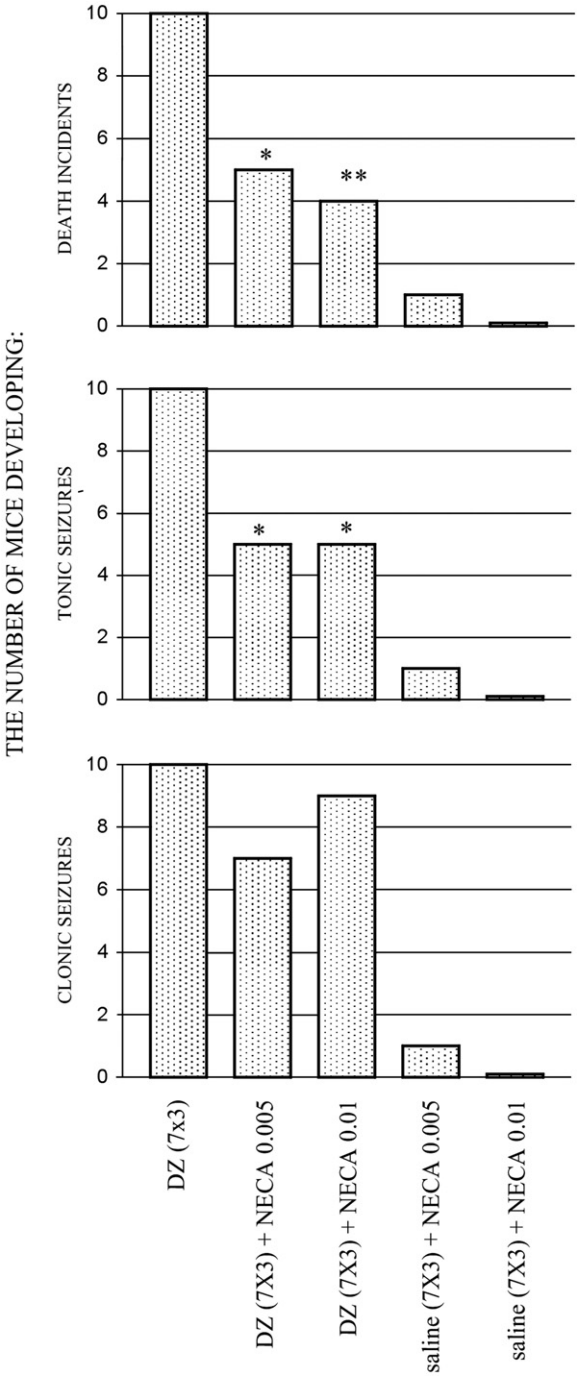

Fig. 4. Effect of NECA (0.005 and 0.01 mg/kg, i.p.) on the development of sensitization to diazepam withdrawal signs. NECA was injected in mice during diazepam-free periods (three, daily injections of NECA in each of that period). The withdrawal signs were induced 48 h after the cessation of diazepam treatment by simultaneous injection of pentetrazole and flumazenil. Data represent the number of mice responding with withdrawal signs. $n=10$, $^{*}P<0.05$, $^{**}P<0.01$ vs sporadically diazepam treated mice (DZ 7 × 3) (the Fisher exact test).

The clear seizure threshold was observed after treatment with pentetrazole alone in saline treated mice. No significant changes in seizure activity were also observed after administration of pentetrazole alone in animals chronically treated with diazepam, both in continuous and sporadic treatment of mice. The changes in seizure activity were not observed in saline treated mice also after the administration of the injections of pentetrazole and flumazenil together (Fig. 1).

In mice sporadically treated with diazepam, the administration of adenosine receptor agonists (CPA, CGS 21680 and NECA) during two diazepam-free periods reduced the diazepam withdrawal signs. CPA (0.025 and 0.05 mg/kg, i.p.) decreased all observed withdrawal signs and the significant attenuations ($P<0.05$) of tonic convulsions and death episodes were recorded after the administration the higher dose of that drug (0.05 mg/kg) (Fig. 2). CGS 21680 (0.1 and 0.2 mg/kg, i.p.) also decreased the number of withdrawal signs. The significant reductions were induced by both used doses of CGS 21680 in the case of tonic convulsions ($P<0.05$ and $P<0.01$, respectively) and death ($P<0.01$) (Fig. 3). Both used doses of NECA (0.005 and 0.01 mg/kg, i.p.) significantly reduced the number of tonic convulsions ($P<0.05$) and death incidents ($P<0.05$, $P<0.01$, respectively) in diazepam sporadically treated mice (Fig. 4).

CPA, CGS 21680 and NECA did not affect the seizure activity in saline treated mice, receiving concomitantly pentetrazole and flumazenil (Figs. 2–4).

4. Discussion

The present experiments were undertaken to investigate the effect of some adenosine receptor agonists on the development of sensitization to diazepam withdrawal signs. The daily and chronic administration of diazepam produced the state of dependence, manifesting as the withdrawal signs. The more intensive withdrawal signs were obtained in the group of animals sporadically treated with diazepam than in continuously treated mice. Thus, in the present experiment, we have observed diazepam withdrawal syndrome precipitated after sporadic treatment with diazepam. The effect of intensification of diazepam withdrawal syndrome precipitated after sporadic treatment with diazepam is referred as the sensitization to withdrawal signs. It is well known, that the withdrawal signs may appear gradually – when drug of abuse is eliminated, or, immediately – when appropriate antagonist is used. In the present study we have induced the diazepam withdrawal signs immediately, by concomitant application of flumazenil–benzodiazepine receptor antagonist, and the subthreshold dose of pentetrazole (a proconvulsive drug). This procedure has been elaborated in our laboratory (Listos et al., 2005, 2006). It has made possible to obtain the most intensive diazepam withdrawal signs. Pentetrazole or flumazenil giving alone has not been enough to induce the similar effects.

The major finding of our experiments is that, the administration of all adenosine receptor agonists during two diazepam drug-free periods in sensitized mice, significantly attenuated their seizure activity. Indeed, CPA, the selective adenosine A_1 receptor agonist, significantly decreased the number of tonic convulsions and death episodes after the administration the higher dose of that drug, and more clear results were obtained by CGS 21680 and NECA, in which the number of tonic convulsions and death was reduced after application of both doses of these drugs. Thus, the most apparent effects were obtained after the stimulation of both adenosine A_1 and A_{2A} receptors and A_{2A} alone. These results support the hypothesis that adenosinergic system is involved in the mechanisms of sensitization to withdrawal signs precipitated after sporadic treatment with diazepam. Thus, accordingly to our previous studies (Listos et al.,

2005, 2006), the present results confirm the modulating role of the adenosinergic system in the mechanisms of benzodiazepine dependence. Moreover, on the authority of the present results, we suppose that adenosine A_{2A} receptor seems to be more involved in the observed effects, because both doses of CGS 21680 and NECA decreased the seizure activity of mice strongly than CPA. However, basing on the obtained results, the role of adenosine A_1 receptors cannot be excluded in the sensitization to diazepam withdrawal signs, because, it is possible, that CPA given at the higher dose then 0.05 mg/kg, would be able to produce stronger effect. Thus, the further studies are necessary to clarify the role of A_1 receptors in the observed effects. Furthermore, it is likely that significant reductions of tonic convulsions and death incidents, but not clonic seizures, observed after the administration of all adenosine ligands, were also associated with low doses of these drugs. We suppose that higher doses of these compounds would be produced the stronger effect on all observed withdrawal signs, but we wanted to exclude the influence of adenosine receptors on another neuronal system.

In summary, taking into account the present results and our previous experiments (Listos et al., 2005), in which we have demonstrated the more important role of adenosine A_1 receptors than A_{2A} receptors in the mechanism of benzodiazepine withdrawal signs we suppose that the appearance of benzodiazepine withdrawal signs and sensitization to that effect may be induce by the different mechanisms.

A variety of addictive drugs appear to exert their rewarding effect via the activation of a common neuronal substrate, especially in mesolimbic dopamine pathways. The abuse liability of benzodiazepines is relatively low in comparison with other abused drugs (morphine, cocaine, amphetamine) and the continued use of benzodiazepine is related to avoiding the withdrawal reaction rather than to the positive reinforcing effects (Allison and Pratt, 2003). Therefore, the mechanisms of benzodiazepine dependence are not fully clarified. Several data demonstrate that the alterations in GABAergic system, like alterations in $GABA_A$ receptor subunit expression or changes in $GABA_A$ receptor density, are mainly responsible for the appearance of benzodiazepine dependence (for Ref. see Allison and Pratt, 2003). On the other hand, Stephens (1995) hypothesized that the chronic treatment with benzodiazepines may induce the excitatory mechanisms, such as glutamatergic system, as part of compensatory effects. Thus, it is possible that the overactivity of glutamatergic system, which may be associated with the alterations in *N*-methyl-D-aspartate (NMDA) receptor subunit expression or changes in binding to this receptor subtypes, may be responsible for the appearance of the benzodiazepine withdrawal signs. Although these mechanisms are more recognized in the ethanol dependence, the similar activity of benzodiazepines and ethanol in the central nervous system supports this hypothesis. Moreover, the other experiments carried out on mice, confirm the glutamatergic theory of diazepam sensitization. In these experiments the increase in sensitivity to pentetrazole-induced seizures, observed during the repeated withdrawals (Ward and Stephens 1998) as well as the attenuating effect of the NMDA receptor antagonist (CGP 39551) in that process (Dunworth and Stephens 1998) have been demonstrated.

The mechanisms by which adenosine receptor agonists affect the sensitization are complex and not fully understood. In the central nervous system Fredholm et al. (2001) has described the close antagonistic interactions of the adenosinergic system with glutamatergic and dopaminergic system — two major systems, which are the most expressed in the sensitization process. Moreover, Fredholm et al. (2001) has also pointed to the presence of adenosine A_{2A} receptors on GABAergic output neurons projecting to the globus pallidus (for Ref. see Fredholm et al., 2001). It is likely that the observed activity of adenosinergic system may result from two pathways: the interaction between adenosine receptors and glutamatergic receptors, which are more expressed during diazepam withdrawal period, or the interaction between adenosine receptors and GABA receptors, which activity is also changed during chronic diazepam treatment. Further studies are necessary to determine the exact pathways of these connections.

In our study, we used the pentetrazole as one of the seizure inducing factors. In numerous experimental studies, pentetrazole is the most frequently used proconvulsive drug. The mechanism of action of pentetrazole is not fully clarified. It is generally accepted that its activity is related to the picrotoxin site of the channel of $GABA_A$ receptors (Huang at al., 2001). Several experiments also propose the involvement of glutamatergic system in the activity of pentetrazole (Corda et al., 1992; Giorgi at al., 1991). Moreover, the close relationship between mechanism of pentetrazole action and adenosinergic system in the central nervous system has also been documented (Homayoun et al., 2001; Pagonopoulou et al., 1993; Psarropoulou et al., 1994). At the present study, we suppose that pentetrazole did not affect the results of our investigation because it was given only at a single, subthreshold dose and the measurement was made immediately.

In summary, it has already been described that chronic treatment with diazepam produced the state of dependence, manifesting mainly as the withdrawal signs. Consistent with these data, the present experiments were designed to further evaluate the possible mechanisms of behavioral sensitization to diazepam withdrawal signs. First, our findings indicate that sporadic treatment with diazepam induces the intensification of the next episode of withdrawal. Secondly, the administration of all adenosine receptor agonists in sensitized mice, during diazepam drug-free periods, significantly attenuated the withdrawal signs, and the adenosine A_{2A} receptors seem to be more involved in that process. Taken together, it is reasonable to conclude that adenosinergic system may play an important role in diazepam-induced neural and behavioral plasticity underlying the development of addiction.

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