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Effects of Tianeptine on Onset Time of Pentylenetetrazole-Induced Seizures in Mice: Possible Role of Adenosine A_1 Receptors

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Depression is a common psychiatric problem in epileptic patients. Thus, it is important that an antidepressant agent has anticonvulsant activity. This study was organized to investigate the effects of tianeptine, an atypical antidepressant, on pentylenetetrazole (PTZ)-induced seizure in mice. A possible contribution of adenosine receptors was also evaluated. Adult male Swiss–Webster mice (25–35 g) were subjects. PTZ (80 mg/kg, i.p.) was injected to mice 30 min after tianeptine (2.5–80 mg/kg, i.p.) or saline administration. The onset times of 'first myoclonic jerk' (FMJ) and 'generalized clonic seizures' (GCS) were recorded. Duration of 600 s was taken as a cutoff time in calculation of the onset time of the seizures. To evaluate the contribution of adenosine receptors in the effect of tianeptine, a nonspecific adenosine receptor antagonist caffeine, a specific A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), a specific $A2_A$ receptor antagonist 8-(3-chlorostyryl) caffeine (CSC) or their vehicles were administered to the mice 15 min before tianeptine (80 mg/kg) or saline treatments. Tianeptine (40 and 80 mg/kg) pretreatment significantly delayed the onset time of FMJ and GCS. Caffeine (10–60 mg/kg, i.p.) dose-dependently blocked the retarding effect of tianeptine (80 mg/kg) on the onset times of FMJ and GCS. DPCPX (20 mg/kg) but not CSC (1–8 mg/kg) blocked the effect of tianeptine (80 mg/kg) on FMJ. Our results suggest that tianeptine delayed the onset time of PTZ-induced seizures via adenosine A_1 receptors in mice. Thus, this drug may be a useful choice for epileptic patients with depression.

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INTRODUCTION

Depression is a very important problem in epileptic patients (Robertson, 1985). However, many antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRI) and tricyclics may lower the seizure threshold or have proconvulsant activity (Hollister, 1978). Thus, selecting a rational and harmless antidepressant therapy for epileptic patients with depression is very important.

Tianeptine is a tricyclic drug that exhibits antidepressant activity in experimental models and clinical trials. It selectively accelerates presynaptic serotonin reuptake at the synaptic cleft (Mennini *et al*, 1987; Fattaccini *et al*, 1990), in contrast to other antidepressant drugs such as SSRIs and tricyclics. Experimental studies have also been showed that tianeptine had some beneficial effects on acute stress-induced structural remodeling in hippocampus involving debranching and shortening of dendrites and suppression of neurogenesis (Watanabe *et al*, 1992; Czéh *et al*, 2001; Rocher *et al*, 2004).

Some tianeptine analogous prolonged the onset of the tonic convulsions and death induced by pentylenetetrazole (PTZ) in mice (Sanchez-Mateo *et al*, 2003). In addition, in a recent study from our laboratory (Ceyhan *et al*, 2005) indicated that tianeptine but not fluoxetine, an SSRI, have a beneficial inhibitory effect on PTZ-induced seizures in rats. In another study from our laboratory indicated that tianeptine has an inhibitory effect on audiogenic seizure in ethanol-withdrawn rats (Uzbay *et al*, 2006). Although these findings imply that tianeptine could have anticonvulsant activity, the mechanism of the anticonvulsant effect of tianeptine was not clarified in these studies. However, in a recent preliminary study, we obtained some indications implying that adenosinergic system may have a role in the effects of tianeptine on PTZ-induced seizures (Uzbay *et al*, 2004).

Adenosine functions as a neuromodulator and presynaptically inhibits the release of many neurotransmitters. It also reduces the rate of spontaneous firing of many neurons in the brain and produces a basal adenosinergic tonus, which has inhibitory effects in general (Fredholm, 1995; McKim, 2000). Adenosine acts through specific G-protein coupled

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receptors and activates A_1 and A_{2A} subtypes of adenosinergic receptors at physiological concentrations. Thus, it can be concluded that A_1 and A_{2A} receptors are responsible for the basal inhibitory adenosinergic tonus (Snyder, 1981; Williams, 1990; Fredholm *et al*, 2001). Besides having a role in many inhibitory central mechanisms, adenosine has also been implicated in arrest of seizures. The anticonvulsant action of adenosine and its analogues has been showed both *in vivo* (Maitre *et al*, 1974; Petersen, 1991) and *in vitro* (Dunwiddie, 1980) studies on rodents. In addition, it has been observed that the levels of endogenous adenosine were dramatically elevated in the brain following seizures (Chin, 1989).

The present study was organized to investigate the effects of tianeptine on PTZ-induced seizures in mice. Then, we aimed to evaluate a possible contribution of adenosine receptors to beneficial effect of tianeptine on PTZ-induced seizures in mice. Thus, we used caffeine, a nonselective blocker of adenosine receptors (Snyder, 1981), 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), a selective blocker of A_1 receptors (De Sarro *et al*, 1999), and 8-(3-chlorostyryl) caffeine (CSC), a selective blocker of A_{2A} receptors for testing a possible relationship between the inhibitory effects of tianeptine on the seizures and adenosinergic receptors.

MATERIALS AND METHODS

Animals and Laboratory

Adult female Swiss–Webster mice (25–35 g) were subjects in the present study. They were housed in a quiet and temperature-and humidity-controlled room ($22 \pm 2^{\circ}$C and $60 \pm 5\%$, respectively) in which a 12-h (light/dark) cycle was maintained (07:00–19:00 light). All experiments were performed at the same time of the day and in the light period (09:00–11:30).

All procedures in the present study are in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health (Washington, DC, USA, 1996). All efforts were made to minimize animal suffering to reduce the number of animals used. The animals were controlled for their pregnancy status. We made sure that the mice selected for the study were not pregnant.

Drugs

Caffeine PTZ, DPCPX and CSC were purchased from Sigma Chemical (USA). Tianeptine was a generous gift from Servier (TR). Caffeine, PTZ and tianeptine were dissolved in 0.9% saline. DPCPX was dissolved in dimethyl sulphoxide (DMSO, Sigma Chemical, USA) and sodium hydroxide (NaOH, 0.1 M), and diluted with saline. The final concentrations at the highest dose were 15 and 8% (v/v) for DMSO and NaOH, respectively. CSC was also dissolved in DMSO and diluted with saline. The final concentration of DMSO was 15% (v/v) at the highest dose. All drugs injected intraperitoneally in a volume of 10 ml/kg. Drug solutions were prepared freshly in the morning.

Experimental Procedures

Mice were assigned into individual groups randomly. Each group had eight animals in the present study. All animals were handled and habituated to the locomotor activity cages before the tests.

To understand which doses of tianeptine are sedative and/or muscle relaxant, we performed the locomotor activity measurments first. Tianeptine (10–160 mg/kg) was administered to the mice and the effects on locomotor activity were evaluated for 30 min by an open-field activity monitoring system (MAY 9908 model—Activity Monitoring System—Commat Ltd., TR). Locomotor activity was recorded as a total of horizontal, vertical and ambulatory activities of the mice. Maximum dose of tianeptine, which did not affect the locomotor activity, was selected as 80 mg/kg. Tianeptine was injected to mice 30 min before the tests.

In subsequent experiments, tianeptine (2.5–80 mg/kg, i.p.) or saline was administered to mice 30 min prior to PTZ (80 mg/kg, i.p.) injection. Immediately after PTZ treatment, mice were placed in a Plexiglas cage and observed for onset times of 'first myoclonic jerk' (FMJ) and 'generalized clonic seizures' (GCS) as previously described (Kaputlu and Uzbay, 1997). The onset times were recorded as seconds. The observation period for PTZ-induced seizures were limited to 30 min. Duration of 600 s was taken as a cutoff time in calculation of the onset time of PTZ-induced seizures. As FMJ and GCS indicate initiation and spreading of the seizures, respectively, we tested and evaluated both parameters involved in the PTZ-induced seizures in the present study.

To evaluate the contribution of adenosine receptors in the effect of tianeptine, a nonspecific adenosine receptor antagonist caffeine, a specific A_1 receptor antagonist DPCPX and a specific A_{2A} receptor antagonist CSC or their vehicles administered to the mice 15 min before tianeptine (80 mg/kg) or saline treatments.

Statistics

The effects of tianeptine on locomotor activity and seizures were evaluated by one-way analysis of variance (ANOVA) test followed by Dunnett's test for *post hoc* comparisons. In addition, the effects of various doses of caffeine and CSC on the anticonvulsant effect of tianeptine (80 mg/kg) were also evaluated by the same statistical protocol. Student's *t*-test was used in comparing saline or vehicle groups with tianeptine (80 mg/kg) group. Student's *t*-test was also used to evaluate the effects of DPCPX. The level of statistical significance was set at $p < 0.05$.

RESULTS

Tianeptine, at the dose of 160 mg/kg, significantly depressed the locomotor activity of mice [$F(5,42) = 5.695$; $p < 0.0001$] (Figure 1). Thus, tianeptine doses selected for the further experiments were lower than 160 mg/kg (ie 40 and 80 mg/kg).

Tianeptine pretreatment significantly delayed the FMJ and GCS onset times at the doses of 40 and 80 mg/kg [$F(6,74) = 16.975$; $p < 0.0001$] (Figure 2a and b), while delayed only the GCS onset time, at the dose of 80 mg/kg [$F(6,69) = 9.551$; $p < 0.0001$] (Figure 2b).

Caffeine (10–60 mg/kg) alone, did not affect the onset times of FMJ and GCS [$F(4,35) = 0.603$ and 0.563, for FMJ and GCS respectively; p-values > 0.05] (Data not shown).

Caffeine (10–60 mg/kg, i.p.) dose-dependently blocked the delaying effect of tianeptine (80 mg/kg) on the onset times

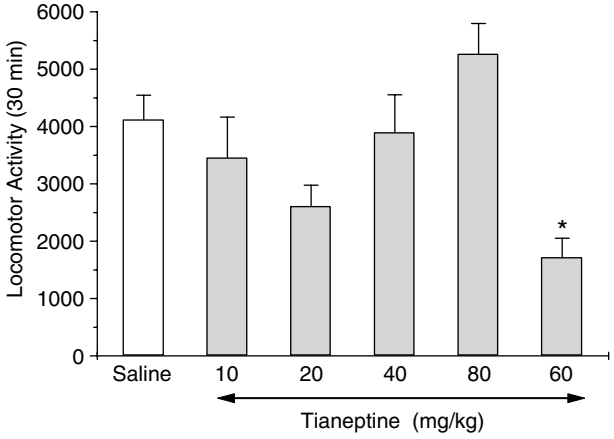

Figure 1 Effect of tianeptine on locomotor activity of mice ($n=8$ for each group; $^{*}p=0.009$, Dunnett's test).

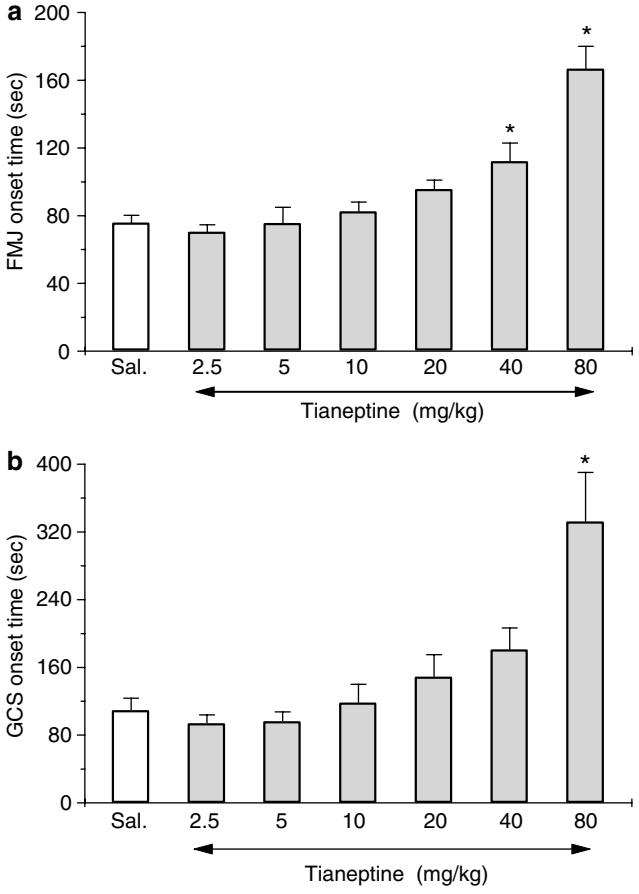

Figure 2 Effects of tianeptine on the onset times of 'first myoclonic jerk' (FMJ) (a), and 'generalised clonic seizures' (GCS) (b) produced by pentylenetetrazole in mice ($^{*}p<0.05$, Dunnett's test; Sal. = Saline control).

of FMJ (Figure 3a) and GCS (Figure 3b) [$F(4,35=10.023$ $p<0.0001$ & $F(4,33)=7.628$; $p=<0.0001$, respectively].

DPCPX (1.25–20 mg/kg) alone, did not affect the FMJ onset time [$F(5,36)=2.469$; $p>0.05$], while reduced the GCS onset time [$F(5,36)=3.544$; $p=0.01$] in PTZ administered mice (data not shown).

DPCPX pretreatment, at the ineffective dose on the FMJ onset time (20 mg/kg), blocked the delaying effect of

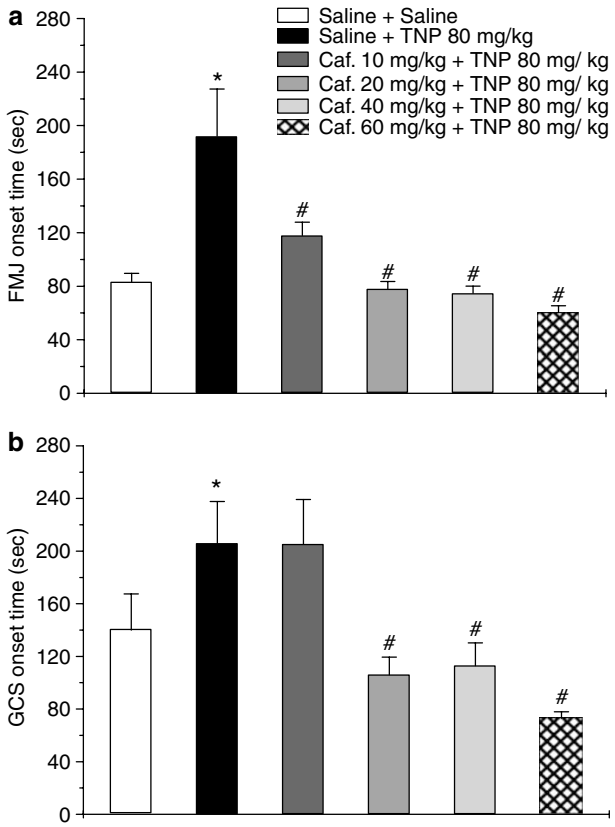

Figure 3 Blocking effect of caffeine on the effects of tianeptine (TNP) on the onset times of 'first myoclonic jerk' (FMJ) (a), and 'generalised clonic seizures' (GCS) (b) produced by pentylenetetrazole (PTZ) (Caf.: Caffeine; $^{*}p<0.05$, Student's *t*-test, significantly different from the 'Saline + Saline' group; $^{\#}p<0.05$, Dunnett's test, significantly different from the 'Saline + TNP 80 mg/kg' group).

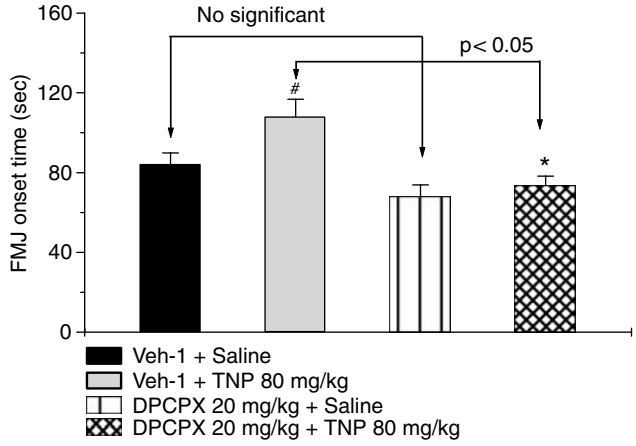

Figure 4 Blocking effect of DPCPX on the effects of tianeptine (TNP) on the onset time of 'first myoclonic jerk' (FMJ) produced by PTZ (Veh-1: Vehicle-1 = DMSO 15% + NaOH 8% (0.1 M); PTZ: pentylenetetrazole; DPCPX: 1,3-dipropyl-8-cyclopentylxanthine; $^{*}p<0.05$, Student's *t*-test, significantly different from the 'Veh-1 + TNP 80 mg/kg' group; $^{\#}p<0.05$, Student's *t*-test, significantly different from the 'Veh-1 + saline' group).

tianeptine (80 mg/kg) on this variable ($p<0.05$, Student's *t*-test) (Figure 4).

CSC alone delayed the FMJ onset time in PTZ administered mice [$F(4,31)=2.847$; $p=0.040$]. *Post hoc* Dunnett's

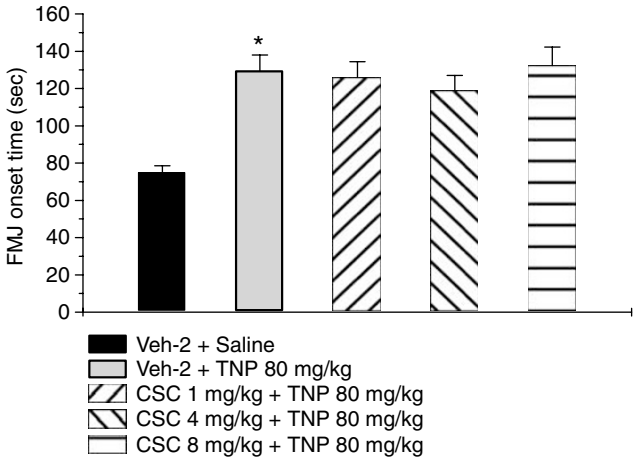

Figure 5 CSC pretreatment did not change the effect of tianeptine (TNP) on the onset time of 'first myoclonic jerk' (FMJ) produced by PTZ (Veh-2: Vehicle-2 = DMSO 15%; PTZ: pentylenetetrazole; CSC: 8-(3-chlorostyryl) caffeine; *$p < 0.05$, Student's *t*-test, significantly different from the 'Veh-2 + TNP 80 mg/kg' group).

tests revealed a significant inhibitory effect at dose of 16 mg/kg ($p = 0.025$) but not at 1, 4 and 8 mg/kg doses ($p = 0.998$, $p = 0.998$ and $p = 0.969$, respectively) (data not shown).

CSC (1–8 mg/kg) pretreatment did not change the effect of tianeptine (80 mg/kg) on FMJ onset time [$F(3,28) = 0.436$; $p = 0.729$] (Figure 5).

Tianeptine was not found effective on mortality of the PTZ-induced seizures in the present study (data not shown).

DISCUSSION

Our results suggest that tianeptine delayed significantly and dose-dependently the onset time of PTZ-induced FMJ and GCS in mice. In addition, the effect of tianeptine on seizures was blocked by caffeine, a nonspecific antagonist of adenosinergic receptors and DPCPX, a selective adenosine A_1 receptor antagonist, but not CSC, a selective A_{2A} antagonist pretreatment. Furthermore, because tianeptine did not change the locomotor activity at effective doses on the seizure, our findings imply that tianeptine acts through its effect on central nervous system, rather than some nonspecific actions such as sedation or muscle relaxation. Overall the data indicate that tianeptine may have an anticonvulsant activity via adenosinergic A_1 receptors in mice. As all animals died after tianeptine treatment like those in controls, we could not evaluate severity of the seizures. According to our results, it seems to be that tianeptine produced some beneficial effects on initiation rather than spreading of PTZ-induced seizures.

In the present study, doses of tianeptine were selected according to our preliminary experiments. Previous studies performed in rodents indicated that tianeptine was effective at lower doses as compared with those using in the present study. For example, it had an anticonvulsant activity in rats at dose of 10 mg/kg (Ceyhan *et al*, 2005). In contrast to rats, we did not observe any significant effect on PTZ-induced seizures by tianeptine treatment in mice up to dose of 40 mg/kg. This situation may be related to different pharmacokinetic profiles of tianeptine in mice and rats. In a previous study from our laboratory, although we found analgesic activity in mice by a lower dose of tianeptine (Uzbay *et al*, 1999), seizures and nociception are different events. Higher doses may be necessary for controlling the seizures. The effective doses of tianeptine used in the present study did also not cause any significant impairment on motor activity in mice. This observation implies, at least, that selected doses for tianeptine and combination studies were not neurotoxic.

Our findings on the delaying effects of tianeptine on PTZ-induced seizures support the results of Ceyhan *et al* (2005) who observed that tianeptine inhibited PTZ-induced seizures in rats. In the present study, we have confirmed those results with tianeptine in mice and extended those results by using adenosine receptor antagonists. These results may be important because this is the first data indicating an interaction between tianeptine and adenosinergic receptors. Previous studies on binding potential of tianeptine to any of the receptors indicated that this drug does not bind to 5-HT_{1A}, 5-HT_{1B}, 5-HT_2 and presynaptic 5-HT receptors, β-adrenoceptors, dopamine D_2 receptors, GABA, glutamate, benzodiazepine, muscarinic and histamine receptors, imipramine binding sites or calcium channels (Mennini *et al*, 1987; Kato and Weitsch, 1988; Ansseau, 1993).

Adenosine has been implicated in the spontaneous and abrupt arrest of seizures. The anticonvulsant effect of adenosine has been observed in various studies. In *in vitro* studies, adenosine depresses seizure activity in hippocampal slices (Dunwiddie, 1980). While in rodents, adenosine and its analogues protect against audiogenic (Maitre *et al*, 1974), chemically induced (Marangos *et al*, 1990; Petersen, 1991) and kindled seizures (Dragunow and Goddard, 1984). Rapid elevations in brain levels of adenosine have also been reported after experimental seizures (Schultz and Lowenstein, 1978; Winn *et al*, 1980) and postseizures in epileptic patients (During and Spencer, 1992).

Adenosine stimulates two major receptor subtypes A_1 and A_{2A}, which are linked to multitude of effectors namely, adenylate cyclase, inositol phosphate, potassium channels, calcium channels, and neurotransmitter release (Williams, 1990). Malhotra and Gupta (1997) suggested that adenosine mediated anticonvulsant effect on PTZ-induced seizures via stimulation of A_1 receptors in rats. In addition, numerous data show that adenosine A_1 receptor density is enhanced in specific brain regions following PTZ-induced seizures (Angelatou *et al*, 1990; Pagonopoulou *et al*, 1993; Tchekalarova *et al*, 2005). De Sarro *et al* (1999) also demonstrated that stimulation of A_1 and A_{2A} receptors plays a role in the inhibition of seizures in audiogenic seizure sensitive mice. These observations clearly indicate that there is a relationship between adenosinergic receptor activation and anticonvulsant activity.

In the present study, we have found that the nonselective A_1/A_2 adenosine receptor antagonist, caffeine and the selective A_1 receptor antagonist, DPCPX, but not A_{2A} antagonist, CSC, pretreatment blocked the delaying effects of tianeptine on the onset time of seizures induced by PTZ. This finding implies that tianeptine could produce the anticonvulsant effect via adenosine A_1 receptors. Furthermore, in contrast to caffeine, DPCPX pretreatment was

ineffective in blocking the effects of tianeptine on the onset time of GCS. It only blocked the effects of tianeptine on PTZ-induced FMJ in mice. CSC pretreatment also did not blocked the effect of tianeptine on GCS. This observation demonstrated that A_1 receptors may have a more significant role in tianeptine effects on the onset time of PTZ-induced FMJ. As both caffeine and DPCPX alone were not effective on FMJ and GCS, their blocking effect on tianeptine are specific and not related to their own seizure-inducing effects. However, more clarification of the relationship between adenosinergic receptors and tianeptine by further studies such as receptor binding analysis may be important. This may provide new therapeutic approaches on tianeptine treatments for clinicians.

In conclusion, our results suggest that tianeptine delayed the onset time of PTZ-induced seizures in mice via adenosinergic A_1 receptors. This drug may be useful for the treatment of epileptic patients with depression.

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