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Effects of adenosine receptor agonists and antagonists on pentylenetetrazole-induced amnesia

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Abstract

The effect of adenosine agents on amnesia induced by pentylenetetrazole was examined in mice. Post-training administration of pentylenetetrazole (50 and 60 mg/kg) disrupted 24-h retention of a single-trial passive avoidance task. The adenosine receptor antagonists, theophylline (2.5–25 mg/kg) and 8-phenyltheophylline (0.5–2 mg/kg), administered 30 min before and just after training at doses which did not affect retention, reduced the amnestic effect of pentylenetetrazole in a dose-dependent manner. Post-training administration of the adenosine A_1 receptor agonists, N^6-cyclohexyladenosine (CHA, 0.1 and 0.5 mg/kg) and N^6-phenylisopropyladenosine (R-PIA, 0.03 and 0.1 mg/kg), but not the adenosine A_2 receptor agonist, 5′-*N*-ethylcarboxamidoadenosine (NECA, 0.01 and 0.001 mg/kg), impaired retention. Nonamnestic doses of CHA and R-PIA potentiated the disruption induced by a lower dose of pentylenetetrazole (40 mg/kg). NECA did not induce any response in this respect. It is suggested that an adenosine A_1 receptor mechanism is involved in amnesia induced by pentylenetetrazole. © 2001 Published by Elsevier Science B.V.

Keywords: Adenosine; Pentylenetetrazole; Passive avoidance; Amnesia; (Mouse)

1. Introduction

A significant number of people with epilepsy experience cognitive difficulties. Pentylenetetrazole is the prototypic systemic convulsant agent, most commonly used for screening antiepileptic drugs (Porter et al., 1984; Fisher, 1989). Single (Banerjee and Das, 1977; Baratti, 1987; Drago et al., 1990; Lazarova et al., 1995) or successive daily (Grecksch et al., 1991; Becker et al., 1992, 1997; Genkova-Papazova and Lazarova-Bakarova, 1995) injections of pentylenetetrazole are associated with significant learning and memory impairments that can be used as experimental models for cognitive problems in epilepsy. Post-training intraperitoneal (i.p.) administration of pentylenetetrazole leads to a disrupted inhibitory avoidance response in mice and rats (Bookin and Pfeifer, 1977; Baratti et al., 1990; Drago et al., 1990; Lazarova et al., 1995). This impairment has been linked to the effects of pentylenetetrazole on the gamma-aminobutyric acid system as well as other neurotransmitter systems that, in turn, disrupt memory consolidation or retrieval (Baratti et al., 1990; Lazarova et al., 1995; Rocha et al., 1996; Becker et al., 1997; Getova et al., 1998). In this regard, opioidergic and serotonergic systems have been implicated in pentylenetetrazole-induced amnesia (Baratti, 1987; Lazarova et al., 1995). It seems that counter-regulatory mechanisms that are activated subsequent to pentylenetetrazole-induced excitatory function may be in part responsible for the cognitive impairment associated with this convulsant agent (Baratti, 1987; Angelatou et al., 1990).

Endogenous adenosine is an important depressant regulator in the central nervous system (CNS) that can act as a natural antiepileptic agent (Winn et al., 1979; Schrader et al., 1980; Lewin and Bleck, 1981; Dragunow, 1988; Kostopoulos et al., 1989). Different types of receptors are believed to mediate the actions of adenosine (Burnstock and Kennedy, 1985; Jacobson et al., 1992). It has been also reported that, subsequent to pentylenetetrazole administration, adenosine-mediated protective activity increases in cortex, hippocampus and striatum, an effect mainly mediated through adenosine A_1 receptors (Angelatou et al., 1990). Therefore, there is an increasing ability of endogenous adenosine to reduce cellular hyperactivity after pentylenetetrazole administration. The adenosine neurotransmitter system is implicated in memory and learning processes (Suzuki et al., 1993; Von Lubitz et al., 1993,

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1996; Zarrindast and Shafaghi, 1994; Riedel et al., 1995; Ohno and Watanabe, 1996; Kopf et al., 1999). While both adenosine A_1 and A_2 receptors are involved in modulation of memory retention and consolidation (Suzuki et al., 1993; Daisley and Rose, 1999; Kopf et al., 1999), activation of adenosine A_1 receptors in the hippocampus leads to working memory dysfunction (Angelatou et al., 1990) and systemic administration of adenosine A_1 receptor agonists decreases retention in a passive avoidance task (Normile and Barraco, 1991; Zarrindast and Shafaghi, 1994). Thus, it is probable that the adenosine neurotransmitter system is involved in pentylenetetrazole-induced amnesia. In the present study, the effect of adenosine receptor agonists, N^6-cyclohexyladenosine (CHA), N^6-phenylisopropyladenosine (R-PIA) and 5′-*N*-ethylcarboxamidoadenosine (NECA), and adenosine receptor antagonists, theophylline and 8-phenyltheophylline, on pentylenetetrazole-induced amnesia was examined using a single trial passive avoidance task in mice.

2. Materials and methods

2.1. Animals

Male albino mice weighing 25–30 g were used. The animals were kept in the animal house with a 12-h light/12-h dark cycle and controlled temperature (22 ± 2 °C). They were given food and water ad libitum. They were housed in groups of 10 in Plexiglas animal cages. Each animal was used once.

2.2. Passive avoidance task

2.2.1. Apparatus

The passive avoidance apparatus consisted of a wooden box ($30 \times 30 \times 40$ cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter set 1 cm apart). A wooden platform ($4 \times 4 \times 4$ cm) was set in the center of the grid floor. Intermittent electric shocks (1 Hz, 0.5 s, 40 V DC) were delivered to the grid floor from an insulated stimulator.

2.2.2. Training

Each mouse was gently placed on the wooden platform. When the mouse stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s (Hiramatsu et al., 1995). This training procedure was carried out between 8:00 a.m. and 1:00 p.m.

2.2.3. Retention test

Twenty-four hours after training, each mouse was placed on the platform again, and the step-down latency was measured with a stopwatch as passive avoidance behaviour. An upper cut-off of 300 s was set. The retention test also was carried out between 8:00 a.m. and 1:00 p.m.

2.3. Treatment

Experiment 1—the animals received post-training (10 min after training) administration of different doses of pentylenetetrazole (20, 40, 50 and 60 mg/kg). Experiments 2 and 3—the animals received theophylline (12.5 and 25 mg/kg) or 8-phenyltheophylline (0.5 and 1mg/kg) 30 min prior to the training session in the presence or absence of pentylenetetrazole (50 mg/kg). Experiments 4 and 5—the animals received theophylline (2.5, 12.5 and 25 mg/kg) or 8-phenyltheophylline (0.5, 1 and 2 mg/kg) immediately after the training session in the presence or absence of pentylenetetrazole (50 mg/kg). Experiment 6 —the animals received post-training CHA (0.1 and 0.5 mg/kg), R-PIA (0.03 and 0.1 mg/kg) or NECA (0.01 and 0.001 mg/kg). Experiment 7—the animals received post-training CHA (0.1 mg/kg), R-PIA (0.03 mg/kg) or NECA (0.01 mg/kg) prior to saline or pentylenetetrazole (40 mg/kg). Ten animals were used in each experimental group.

2.4. Drugs

Theophylline, N^6-cyclohexyladenosine (CHA), N^6-phenylisopropyladenosine (R-PIA), 5′-*N*-ethylcarboxamidoadenosine (NECA), 8-phenyltheophylline and pentylenetetrazole (Sigma, UK) were dissolved in 0.9% saline. All drugs were administered i.p. in a volume of 10 ml/kg.

2.5. Data analysis

The retention latencies are expressed as the median and 95% confidence intervals. The data were analyzed with the Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) followed by the Mann–Whitney *U*-test (Norman and Streiner, 2000). The criterion for statistical significance was $P < 0.05$.

3. Results

3.1. Effect of pentylenetetrazole on the retention of a passive avoidance task

Fig. 1 shows the effect of different doses of pentylenetetrazole (20, 40, 50 and 60 mg/kg) 10 min after training. A significant drug effect was found for retention latency, $H(4) = 34.97$, $P < 0.0001$ (Kruskal–Wallis one-way ANOVA). Analysis of the responses of animals in the individual dose groups with the Mann–Whitney *U*-test showed that pentylenetetrazole (at the 50 and 60 mg/kg doses) significantly shortened the step-down latencies compared to those of saline-treated animals.

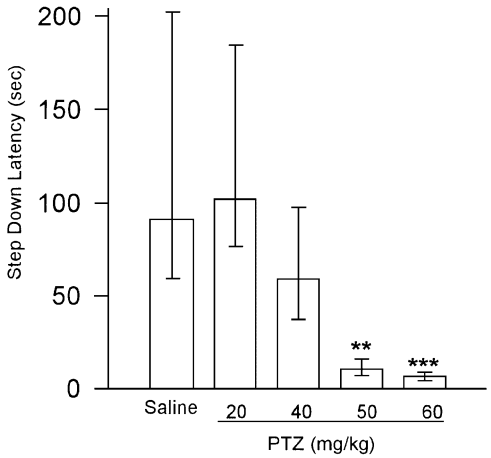

Fig. 1. Effect of different doses of pentylenetetrazole on step-down latencies in the retention test. Pentylenetetrazole was administered i.p. 10 min after training session. Each value represents the median and 95% confidence interval for 10 animals. $^{**}P < 0.05$, $^{***}P < 0.001$ compared to saline group.

3.2. Effects of pre-training and post-training administration of adenosine receptor antagonists on pentylenetetrazole-induced amnesia

Pre-training administration of theophylline (12.5 and 25 mg/kg) or 8-phenyltheophylline (0.5 and 1 mg/kg) combined with post-training saline had no significant effect on retention latency. The same doses of antagonists attenuated the amnesia induced following pentylenetetrazole (50 mg/kg) administration, [theophylline; $H(5) = 28.78$, $P < 0.0001$ and 8-PT; $H(5) = 36.40$, $P < 0.0001$] (Fig. 2) (Kruskal–Wallis one-way ANOVA). Moreover, administration of theophylline (2.5, 12.5 and 25 mg/kg) or 8-phenyltheophylline (0.5, 1 and 2 mg/kg) just after training did not change the retention latency, whereas both drugs antagonized the pentylenetetrazole-induced decrease in retention latency completely and in a dose-dependent manner, [theophylline; $H(7) = 46.54$, $P < 0.0001$ and 8-PT; $H(7) = 30.07$, $P < 0.0001$] (Fig. 3) (Kruskal–Wallis one-way ANOVA).

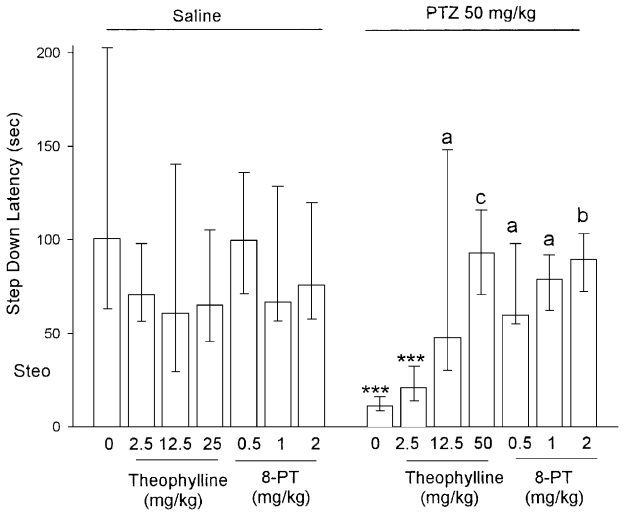

Fig. 3. Effect of post-training administration of theophylline or 8-phenyltheophylline on step-down latencies in the retention test in the presence or absence of pentylenetetrazole. Theophylline or 8-phenyltheophylline was administered immediately after training and pentylenetetrazole or saline was administered 10 min after training. Each value represents the median and 95% confidence interval for 10 animals. $^{***}P < 0.001$ compared to respective saline control group. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ compared to pentylenetetrazole control group.

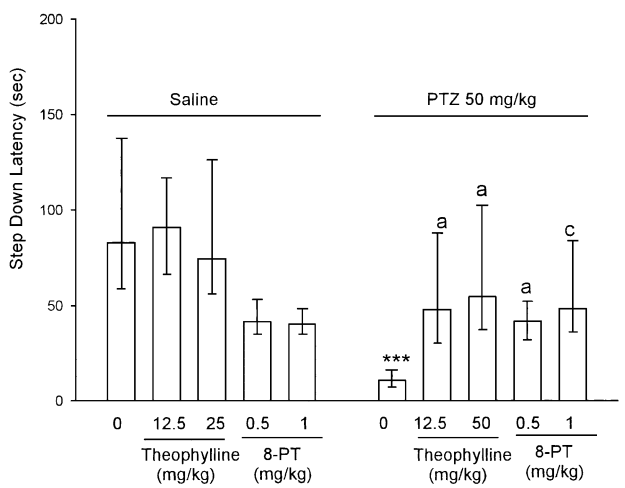

Fig. 2. Effect of pre-training administration of theophylline or 8-phenyltheophylline on step-down latencies in the retention test in the presence or absence of pentylenetetrazole. Theophylline or 8-phenyltheophylline was administered 30 min before training and pentylenetetrazole or saline was administered 10 min after training. Each value represents the median and 95% confidence interval for 10 animals. $^{***}P < 0.001$ compared to respective saline control group. $^{a}P < 0.05$, $^{b}P < 0.001$ compared to pentylenetetrazole control group.

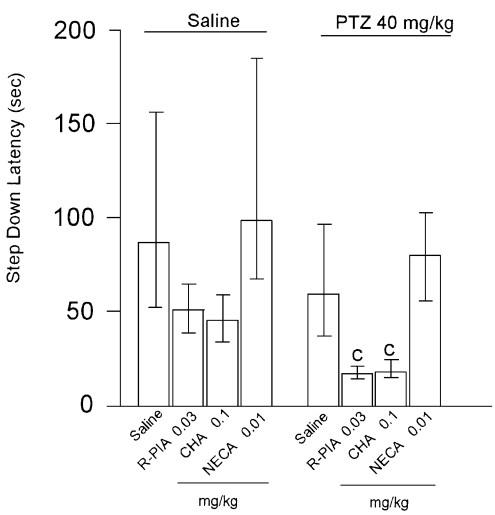

Fig. 4. Effect of post-training administration of R-PIA, CHA and NECA on step-down latencies in the retention test in the presence or absence of pentylenetetrazole (40 mg/kg). R-PIA, CHA and NECA were administered immediately after training and 10 min prior to pentylenetetrazole or saline. Each value represents the median and 95% confidence interval for 10 animals. $^{c}P < 0.001$ compared to pentylenetetrazole control group.

Table 1
Effect of post-training administration of adenosine receptor agonists on retention latency of mice in a passive avoidance task

Treatment	Dose (mg/kg)	Step-down latency (s)
Saline	–	98 (54.45–191.35)
CHA	0.1	45 (33.68–58.91)
CHA	0.5	20 (15.10–23.29)[a]
R-PIA	0.03	51 (38.33–64.66)
R-PIA	0.1	24 (19.47–29.52)[a]
NECA	0.001	100 (79.45–145.55)
NECA	0.01	98.50 (67.61–185.19)

Mice were given saline, CHA, R-PIA or NECA immediately after training session. All values are expressed as median and 95% confidence intervals for 10 animals.

[a] $P < 0.001$ compared to saline group.

3.3. Effects of post-training administration of adenosine receptor agonists on the retention of a passive avoidance task

The effect of post-training administration of adenosine receptor agonists CHA (0.1 and 0.5 mg/kg), R-PIA (0.03 and 0.1 mg/kg) and NECA (0.001 and 0.01 mg/kg), on retention latency were evaluated. CHA and R-PIA decreased retention at the higher dose used $H(2) = 22.37$, $P < 0.0001$ and $H(2) = 21.18$, $P < 0.0001$, respectively (Table 1) (Kruskal–Wallis one-way ANOVA followed by Mann–Whitney *U*-test). NECA did not induce any significant change in retention latency, $H(2) = 0.33$, $P > 0.05$ (Table 1) (Kruskal–Wallis one-way ANOVA).

3.4. Effects of pre-treatment with adenosine receptor agonists on retention in mice receiving an ineffective dose of pentylenetetrazole

To examine the effect of pre-treatment with adenosine receptor agonists on pentylenetetrazole-induced amnesia, a noneffective dose of each agonist (0.1 mg/kg CHA, 0.03 mg/kg R-PIA and 0.01 mg/kg NECA) was chosen and administered just after training prior to post-training pentylenetetrazole (at noneffective dose of 40 mg/kg). The effect of each agonist on pentylenetetrazole-treated mice was independently assessed by Kruskal–Wallis one-way ANOVA. CHA and R-PIA significantly potentiated the retention impairment induced by pentylenetetrazole, $H(3) = 19.76$, $P < 0.0001$ and $H(3) = 22.85$, $P < 0.0001$, respectively (Fig. 4). NECA had no significant effect on latency in mice treated with 40 mg/kg pentylenetetrazole, $H(3) = 4.28$, $P > 0.05$ (Fig. 4).

4. Discussion

The present results indicate that pentylenetetrazole-induced amnesia can be reduced by adenosine receptor antagonist pre-treatment. Moreover, the combination of adenosine A1 receptor agonists with a nonamnestic dose of pentylenetetrazole impairs retention. Our results are in accordance with previous reports showing that subconvulsive doses of pentylenetetrazole (20 and 40 mg/kg) have no significant effect on retention latency while higher doses of the drug (50 and 60 mg/kg) induce a dramatic impairment of memory (Palfai and Kurtz, 1976; Viu et al., 2000).

It has been proposed that adenosine mechanisms, specially A_1 receptors, are involved in in vitro and in vivo models of cognitive impairment (Alzheimer et al., 1989; Tanaka et al., 1990; Normile and Barraco, 1991; Zarrindast and Shafaghi, 1994; Tabata et al., 2001). In the present study, immediate post-training administration of the adenosine receptor agonists CHA and R-PIA, but not NECA, impaired step-down passive avoidance retention in a dose-dependent manner. The data are consistent with those obtained by others (Suzuki et al., 1993; Normile and Barraco, 1991) showing that R-PIA has an amnestic effect and that a highly selective adenosine A_1 receptor agonist, N^6-cyclopentyladenosine impairs retention. Since the typical potency profile of adenosine A_1 receptor-mediated responses is CHA = R-PIA > NECA > S-PIA, and for adenosine A_2 receptor-mediated responses the typical profile is NECA > CHA = R-PIA > S-PIA (Jacobson et al., 1992; Moreau and Huber, 1999), it can be deduced that an adenosine A_1 receptor mechanism is involved in impairment of passive avoidance retention by adenosine receptor agonists. In the present study, post-training administration of nonamnestic doses of adenosine receptor agonists was used to assess their possible potentiation of pentylenetetrazole-induced amnesia. CHA and R-PIA, but not NECA, significantly potentiated the effect of a nonamnestic dose of pentylenetetrazole (40 mg/kg) on retention. The finding may indicate the involvement of an adenosine A_1 mechanism in pentylenetetrazole-induced amnesia.

Adenosine receptor antagonists, theophylline or 8-phenyltheophylline, administered 30 min prior to training had no significant effect on retention. Other researchers have also shown that theophylline and caffeine (Winsky and Harvey, 1987) and 8-cyclopentyl-1,3-dipropylxanthine (DPCPX; a highly selective antagonist for adenosine A_1 receptors) (Normile and Barraco, 1991) do not alter the acquisition of passive avoidance learning. However, our previous study showed that adenosine receptor antagonists impair acquisition at doses higher than those used here (Zarrindast et al., 1995). Pre-treatment administration of either of the antagonists significantly decreased pentylenetetrazole-induced retrograde amnesia in a dose-dependent manner. A similar effect was observed after post-training administration of the antagonists prior to pentylenetetrazole. Although both antagonists are adenosine receptor blockers, 8-phenyltheophylline is 100 times more potent to cause adenosine A_1 than A_2 receptor blockade, while theophylline acts almost nonspecifically (Jacobson et al., 1992). Earlier work has shown that immediate post-train-

ing administration of caffeine and a selective adenosine A_2 receptor antagonist, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-*e*]-1, 2, 4-triazolo-[1, 5-*c*]-pyrimidine (SCH 58261) facilitates, while administration of an adenosine A_1 receptor antagonist, DPCPX, does not affect retention (Kopf et al., 1999). Our data showed that post-training administration of adenosine receptor antagonists per se had no effect on retention. Furthermore, adenosine A_1 receptor antagonists ameliorate the shortened retention latency induced by the adenosine A_1 receptor agonist, R-PIA (Suzuki et al., 1993), providing evidence for an amnestic function of A1 receptors. Thus, our finding that noneffective doses of theophylline and 8-phenyltheophylline can inhibit pentylenetetrazole-induced amnesia implies that endogenous adenosine, acting through A_1 receptors, may be involved in this phenomenon. Brain adenosine levels increase dramatically within seconds following the onset of several kinds of seizures experimentally induced in experimental animals (Winn et al., 1979; Schrader et al., 1980; Lewin and Bleck, 1981; Angelatou et al., 1990) and during post-seizure period in epileptic patients (During and Spencer, 1992). Acute administration of convulsant doses of pentylenetetrazole leads to activation of the adenosine system in brain areas involved in learning and memory (Angelatou et al., 1990). Interestingly, the antiepileptic role of endogenous adenosine activated after pentylenetetrazole administration is mainly mediated via adenosine A_1 receptors (Angelatou et al., 1990). Whether activation of adenosine defence mechanism(s), following pentylenetetrazole-induced excitation, is responsible for pentylenetetrazole-induced cognitive impairment should be further investigated. However, the complete reversal of pentylenetetrazole-induced amnesia by 8-phenyltheophylline supports this hypothesis.

It should be considered that the adenosine receptor agonists induce significant protection against pentylenetetrazole-induced seizures (Malhorta and Gupta, 1997) but enhance the pentylenetetrazole-induced cognitive impairment. In contrast, adenosine receptor antagonists known to enhance the EEG and behavioural effects of pentylenetetrazole (Cutrufo et al., 1992) can attenuate the pentylenetetrazole-induced cognitive impairment. Regarding these results, it may be assumed that cognitive impairments induced by pentylenetetrazole are not necessarily linked with pentylenetetrazole-induced seizures. Earlier work has shown that gangliosides have no anticonvulsive effect in pentylenetetrazole-treated rats but exert an improving effect on the pentylenetetrazole-induced learning deficit. In addition, prevention of pentylenetetrazole-induced seizures by diazepam is not protective against the pentylenetetrazole-induced learning impairment. Thus, it may be suggested that suppression of seizures is not sufficient to prevent cognitive disturbances in epilepsy. Results of this study provide some evidence for the involvement of an adenosine A_1 receptor mechanism in amnesia induced by pentylenetetrazole. The involvement of adenosine receptors in other cognitive impairments observed in different seizure models, including pentylenetetrazole kindling, deserves further investigation.

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