

Original Article

Effect of Brewer's Yeast-Induced Pyrexia on Aminophylline-Elicited Convulsions in Mice

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Theophylline-associated convulsions have been observed most frequently in children with fever, but the mechanism is not fully understood. In this study, we investigated the basic mechanism of aminophylline [theophylline-2-ethylenediamine]-induced convulsions and the effects of Brewer's yeast-induced pyrexia in mice. Diazepam (5–10 mg/kg, i.p.), a benzodiazepine receptor agonist, significantly prolonged the onset and significantly decreased the incidence of convulsions induced by aminophylline (350 mg/kg, i.p.). However, the gamma aminobutyric acid (GABA)_A receptor agonist muscimol (1–4 mg/kg, i.p.), the GABA_B receptor agonist baclofen (2–4 mg/kg, i.p.) and the *N*-methyl-D-aspartic acid receptor antagonist dizocilpine (0.1–0.3 mg/kg, i.p.) failed to protect against the convulsions. 20% Brewer's yeast (0.02 ml/g, s.c.) increased body temperature by 1.03°C, and also significantly shortened the onset and significantly increased the incidence of convulsions induced by aminophylline. The anti-convulsant action of diazepam (2.5–10 mg/kg, i.p.) on the convulsions induced by aminophylline was reduced by Brewer's yeast-induced pyrexia. The proconvulsant actions of the GABA_A receptor antagonists picrotoxin (3–4 mg/kg, i.p.) and pentylenetetrazol (40–60 mg/kg, i.p.) were enhanced by Brewer's yeast. These results suggest that the anticonvulsant action of diazepam against aminophylline is reduced by Brewer's yeast-induced pyrexia, and that GABA_A receptors are involved in the aggravation of the convulsions by Brewer's yeast in mice.

Key words: theophylline, seizures, pyrexia, Brewer's yeast, GABA_A receptor

Theophylline is widely used as a bronchodilator in neonatal apnea, but it runs the risk of toxicity and associated convulsions [1]. Therapeutic drug monitoring of theophylline is thus important to avoid this adverse reaction [2]. However, several reports have shown that theophylline at therapeutic doses occasionally induces convulsions and status epilepticus

in children, particularly at pre-school age [1, 3]. The current Japanese Asthma Guidelines (2005) recommend that theophylline should be avoided in children under 6 months of age, and in children more than 6 months of age with prior seizures and/or other neurological abnormalities [4]. In addition, in children, it is recommended that the dosage of theophylline should be reduced or the drug withdrawn, if fever occurs [4].

Theophylline is a very potent central nervous system stimulant, and most of its pharmacological effects

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can be linked to the blockade of adenosine receptors and inhibition of phosphodiesterase. Benzodiazepines are widely used as anticonvulsants against theophylline-induced convulsions, and it is well known that benzodiazepines are agonists for the gamma-aminobutyric acid (GABA)_A receptor complex [5]. Previous studies using various models of convulsions have shown the involvements of adenosine receptor [6–8], GABA receptor [9], benzodiazepine receptor [10], and *N*-methyl-D-aspartic acid (NMDA) receptor [11, 12] in the proconvulsant action of theophylline. However, the precise mechanisms of the proconvulsant effect of theophylline underlying fever are not clear.

The first aim of this study was to evaluate the basic mechanism of theophylline-induced convulsions. The second aim was to clarify the effect of fever on the proconvulsant effect. Aminophylline is a water-soluble theophylline compound with ethylenediamine. It is well documented that the central nervous system stimulant properties of aminophylline are due to its theophylline component, since ethylenediamine has no convulsive potential [13]. Thus, in this study, to evaluate the basic mechanism of theophylline-induced convulsions, the convulsion-ameliorating effects of drugs acting on adenosine, NMDA, GABA and benzodiazepine receptors were investigated in mice. On the other hand, Brewer's yeast-induced pyrexia has been used as a screening tool for antipyretic agents in rodents [14]. Therefore, we investigated the effects of fever on aminophylline-induced convulsions using the Brewer's yeast-induced pyrexia. In addition, to clarify the involvement of GABA_A receptors in the proconvulsant effect of fever, the changes in the threshold of convulsion induced by GABA_A receptor antagonists were investigated.

Materials and Methods

Animals. Male ddY mice (at 6–7 weeks of age) were obtained from SLC Co., Ltd., (Shizuoka, Japan). All of the animals were housed in groups of five per plastic cage (18 × 44 × 27 cm) in a room maintained at 22 ± 2°C under a 12/12h light/dark cycle with lights on at 07:00 a.m. The experimental protocol was conducted according to the Guidelines of the Ethics Review Committee for Animal Experimentation of Ehime University Medical School.

Drugs. The following drugs were used: aminophylline (theophylline-2-ethylenediamine, Neophylline[®] injection Eisai Co., Tokyo, Japan), 2-chloro-N⁶-cyclopentyladenosine (CCPA, adenosine A₁ receptor agonist Sigma-Aldrich Inc., St. Louis, MO, USA), N⁶-cyclopentyladenosine (CPA, adenosine A₁ receptor agonist Sigma-Aldrich Inc.), 5'-(*N*-cyclopropyl) carboxamidoadenosine (CPCA, adenosine A₂ receptor agonist Sigma-Aldrich), dizocilpine maleate (NMDA receptor antagonist Sigma-Aldrich), muscimol (GABA_A receptor agonist Sigma-Aldrich), (±) baclofen (GABA_B receptor agonist Sigma-Aldrich), pentylentetrazol (GABA_A receptor antagonist Wako Pure Chemical Industries, Ltd. Osaka, Japan), picrotoxin (GABA_A receptor antagonist Sigma-Aldrich) and diazepam (benzodiazepine receptor agonist Wako). Diazepam was dissolved in 10% polyethylene glycol. The other drugs were dissolved in saline. All drugs were injected i.p. at a volume of 0.1 ml per 10 g body weight.

Induction of pyrexia. Induction of pyrexia was based on a method of Bhat *et al.* [14]. After recording the rectal temperature of each of the animals in a batch, pyrexia was induced by subcutaneous injection of 20% Brewer's yeast suspension (Sigma-Aldrich) in the neck scruff at a volume of 0.02 ml/g body weight. Animals were fasted and 18h later, on the following day, the rectal temperature of each animal was recorded by a digital thermometer. The mice exhibiting a rise in temperature of more than 0.8°C were considered pyretic [14] and all the pyretic animals were randomly administered saline or drugs.

Aminophylline-induced convulsions. Experiments were carried out with graded single doses of aminophylline from 250–350 mg/kg administered i.p. to mice. After injection, the mice were put into individual plastic cages and observed for 60 min to examine the following parameters:

- Percent (%) of animals having clonic convulsions
- Latency of onset of clonic convulsions (min)

In mice which did not show any convulsions during the observation period of 1 h, the convulsion latency was taken as 60 min for the purpose of data analysis. On the basis of the results obtained with various doses of aminophylline, a dose producing clonic convulsions in 100% of animals was selected for subsequent experiments to investigate the modulatory effects of

different drugs. Aminophylline was injected 30 min after the treatments (i.p.) with CCPA, CPA, CPCA, muscimol, baclofen, dizocilpine, diazepam and saline.

Convulsions induced by GABA_A receptor antagonists. To examine changes in the threshold of convulsion induced by GABA_A receptor antagonists, mice were treated with various doses of picrotoxin (3–4 mg/kg) and pentylenetetrazol (40–60 mg/kg) 18 h after the administration of 20% Brewer's yeast (0.02 ml/g, s.c.) or saline. The mice were then placed in isolated cages and observed for 60 min after the administration of each convulsant drug.

Statistical analysis. All mean values of the data were presented with their standard error (S.E.). The latency of clonic convulsions by aminophylline-induced convulsions was analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test or Tukey's test. The incidence of clonic convulsions was assessed for significance by the Chi-squared test for independence. For the analysis of convulsion latency in saline- or Brewer's yeast-treated mice, a two-way ANOVA with pyrogen factor and drug factor was used. Whenever the pyrogen factor or the interaction of pyrogen factor \times drug factor was significant, *post hoc* comparisons were performed with the Student's *t*-test. The criterion for statistical significance was set at $p < 0.05$.

Results

Convulsant effect of aminophylline.

Aminophylline (250–350 mg/kg, i.p.) dose-dependently induced clonic convulsions in mice (Fig. 1). The convulsions were characterized by a raised tail, relatively wild running, and violent body movement followed by loss of the righting reflex and finally extension of the hind limbs.

Convulsion-ameliorating effects of drugs acting on adenosine, NMDA, GABA and benzodiazepine receptors. A benzodiazepine receptor agonist, diazepam (5–10 mg/kg, i.p.), significantly prolonged the onset of aminophylline (350 mg/kg, i.p.)-elicited convulsions, and it significantly reduced the number of animals convulsing (Table 1). However, the adenosine A₁ receptor agonists CCPA (1–10 mg/kg, i.p.) and CPA (3–20 mg/kg, i.p.), the adenosine A₂ receptor agonist CPCA (3–20 mg/kg, i.p.), the GABA_A receptor agonist muscimol (1–4 mg/kg, i.p.), the GABA_B receptor agonist baclofen (2–4 mg/kg, i.p.) and the NMDA receptor antagonist dizocilpine (0.1–0.3 mg/kg, i.p.) did not significantly alter aminophylline convulsions.

Effects of Brewer's yeast on body temperature. Subcutaneous administration of 20% Brewer's yeast (0.02 ml/g) induced a significant increase in rectal temperature of saline-treated control mice ($1.03 \pm 0.17^\circ\text{C}$, $n = 10$, $p < 0.01$, paired Stu-

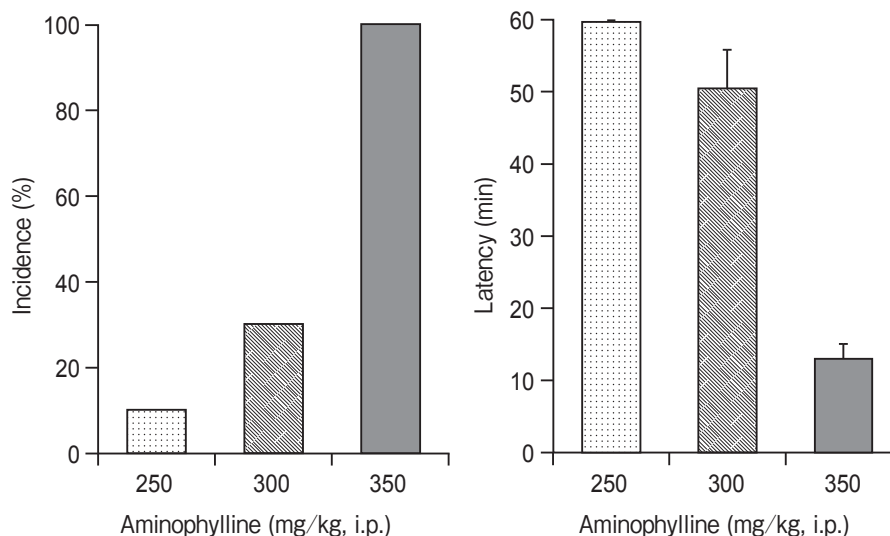


Fig. 1 Convulsant effect of aminophylline in mice. Each column represents the incidence (%) and the mean latency (min) with S.E.M. of convulsions induced by aminophylline (250–350 mg/kg, i.p.) in mice ($n = 10$).

Table 1 Effects of drugs acting on adenosine, NMDA, GABA and benzodiazepines receptors against aminophylline-induced convulsions in mice

Drug and dose (mg/kg)		No. convulsed/ no. used	Latency of clonic convulsion (min) (mean \pm S.E.M.)
Saline	—	10/10	18.5 \pm 2.95
CCPA	1	9/10	17.7 \pm 5.00
	3	10/10	17.6 \pm 1.55
	10	9/10	23.6 \pm 4.29
Saline	—	10/10	13.3 \pm 1.96
CPA	3	10/10	10.0 \pm 0.82
	10	10/10	14.7 \pm 2.48
	20	10/10	11.9 \pm 0.69
CPCA	3	9/10	19.8 \pm 5.04
	10	9/10	31.4 \pm 6.29
	20	9/10	19.6 \pm 4.88
Muscimol	1	10/10	22.1 \pm 4.28
	2	7/10	29.9 \pm 6.85
	4	9/10	23.7 \pm 5.71
Baclofen	2	9/10	17.6 \pm 5.31
	4	8/10	25.7 \pm 6.36
Dizocilpine	0.1	10/10	19.5 \pm 3.26
	0.3	7/10	17.9 \pm 2.28
Diazepam	5	0/10**	60.0 \pm 0.0**
	10	0/10**	60.0 \pm 0.0**

** $p < 0.01$ versus saline control (Dunnett's test).

** $p < 0.01$ versus saline control (Chi-squared test).

All mice were injected aminophylline (350 mg/kg, i.p.) 30 min after the drug treatments (i.p.).

dent's *t*-test) in comparison to the initial rectal temperature 18 h before ($37.49 \pm 0.24^\circ\text{C}$). The other groups of mice also showed significant increases in rectal temperature by the administration of 20% Brewer's yeast (data not shown).

Effects of aminophylline-induced convulsions in Brewer's yeast-treated mice. The Brewer's yeast significantly increased the incidence of convulsions induced by aminophylline (200–300 mg/kg, i.p.) (Fig. 2). Two-way ANOVA revealed that Brewer's yeast treatment significantly shortened the onset of the convulsions induced by aminophylline [pyrogen: $F(1, 52) = 10.063$, $p < 0.001$; drug: $F(2, 52) = 9.406$, $p < 0.001$; interaction: $F(2, 50) = 1.495$, $p > 0.05$]. The *post hoc* comparison using the Student's *t*-test revealed significant differences in the latency of the convulsions at doses of 250 and 300 mg/kg of aminophylline.

Effects of diazepam on aminophylline-induced convulsions in Brewer's yeast-treated mice. The anticonvulsant action of diazepam (2.5–

10 mg/kg, i.p.) on convulsions induced by aminophylline (350 mg/kg, i.p.) was reduced by 20% Brewer's yeast. There was no significant difference in the incidence of convulsions, but the incidence tended to be higher in the Brewer's yeast-treated group compared with the saline-control group Fig. 3. Diazepam dose-dependently prolonged the onset of aminophylline-elicited convulsions [pyrogen: $F(1, 56) = 9.615$, $p < 0.01$; drug: $F(2, 59) = 37.824$, $p < 0.0001$; interaction: $F(2, 54) = 0.776$, $p > 0.05$]. A significant difference ($p < 0.05$) was shown at a dose of 5 mg/kg of diazepam.

Effects of pentylenetetrazol- and picrotoxin-induced convulsions in Brewer's yeast-treated mice. Figs. 4 and 5 illustrate the effect of Brewer's yeast on convulsions induced by GABA_A receptor antagonists in mice. Pentylenetetrazol (40–60 mg/kg, i.p.) dose-dependently produced clonic convulsions, and the incidence of convulsions was significantly higher ($p < 0.01$) with pentylenetetrazol at a dose of 40 mg/kg in Brewer's yeast-treated mice. The

latency of convulsions tended to be shorter at this dose of pentylenetetrazol in Brewer's yeast-treated mice, but two-way ANOVA showed no significant difference statistically [pyrogen: $F(1, 66) = 2.271, p > 0.05$; drug: $F(2, 68) = 5.311, p > 0.05$; interaction: $F(2, 54) = 2.362, p > 0.05$].

Picrotoxin (3-4 mg/kg, i.p.) elicited clonic convul-

sions in a dose-dependent manner. Brewer's yeast significantly shortened the onset of the convulsions [pyrogen: $F(1, 56) = 9.079, p < 0.01$; drug: $F(2, 56) = 14.796, p < 0.0001$; interaction: $F(2, 54) = 2.656, p > 0.05$]. The *post hoc* comparison using the Student's *t*-test revealed a significant reduction in the latency of convulsions at a dose of 3.5 mg/kg of picrotoxin.

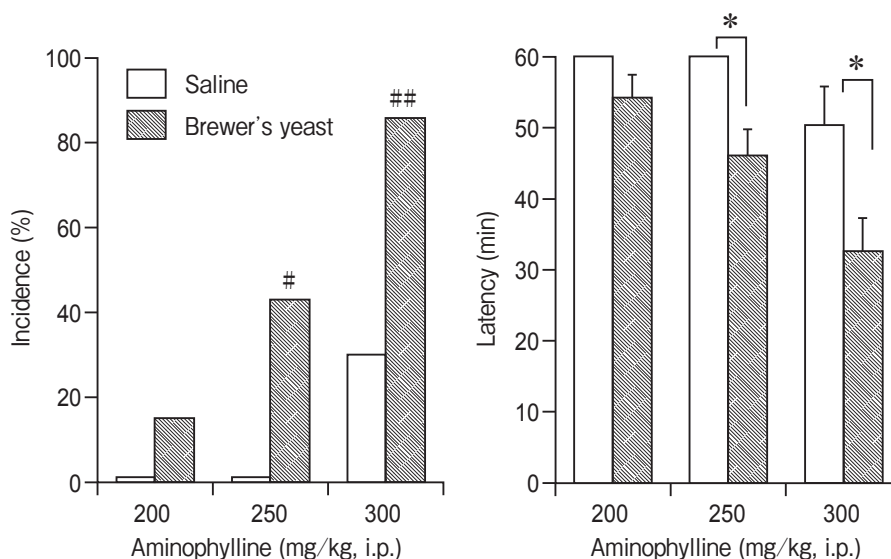


Fig. 2 Aminophylline-induced convulsions in Brewer's yeast-treated mice. Each column represents the incidence (%) and the mean latency (min) with S.E.M. of aminophylline-induced convulsions in saline- or Brewer's yeast-treated mice ($n = 10-18$). # $p < 0.05$, ## $p < 0.01$ (Chi-squared test), * $p < 0.05$ (two-way ANOVA followed by the Student's *t*-test).

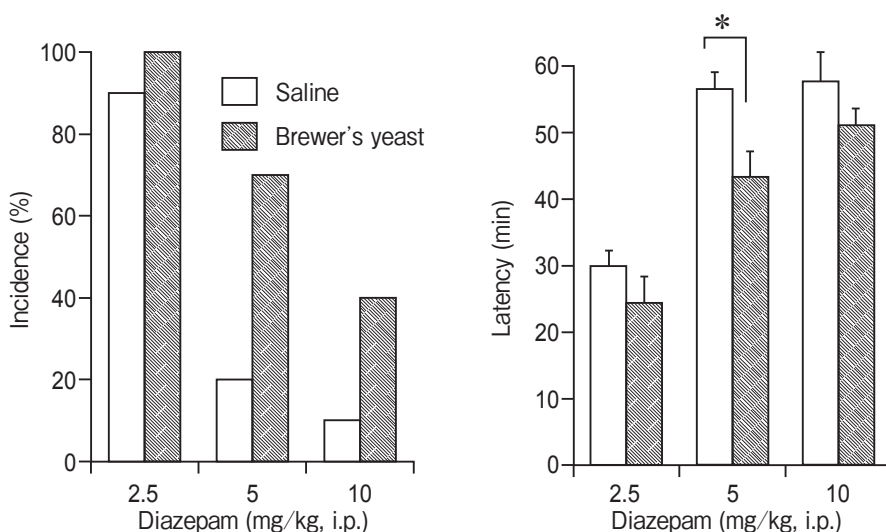


Fig. 3 Anticonvulsant effect of diazepam on aminophylline-induced convulsions in Brewer's yeast-treated mice. Each column represents the incidence (%) and the mean latency (min) with S.E.M. of aminophylline (350 mg/kg, i.p.)-induced convulsions in saline- or Brewer's yeast-treated mice ($n = 10$). * $p < 0.05$ (two-way ANOVA followed by the Student's *t*-test).

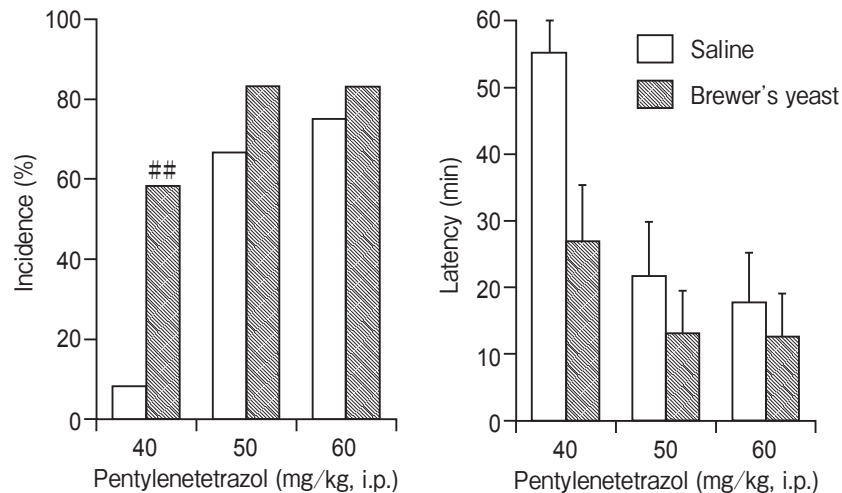


Fig. 4 Pentylentetrazol-induced convulsions in Brewer's yeast-treated mice. Each column represents the incidence (%) and the mean latency (min) with S.E.M. of pentylentetrazol-induced convulsions in saline- or Brewer's yeast-treated mice ($n=12$). ^{##} $p < 0.01$ (Chi-squared test).

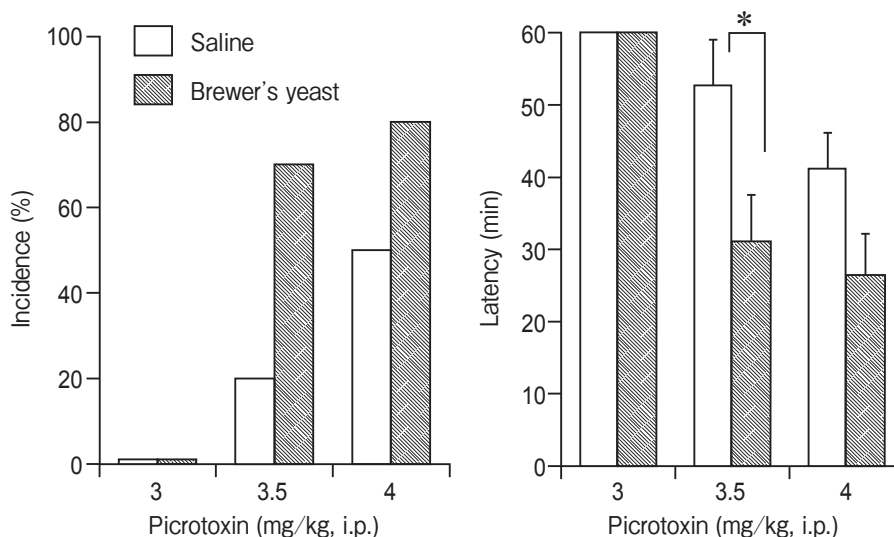


Fig. 5 Picrotoxin-induced convulsions in Brewer's yeast-treated mice. Each column represents the incidence (%) and the mean latency (min) with S.E.M. of picrotoxin-induced convulsions in saline- or Brewer's yeast-treated mice ($n=10$). ^{*} $p < 0.05$ (two-way ANOVA followed by the Student's t -test).

Discussion

Fever not only evokes febrile seizures but also increases the risk of theophylline-induced convulsions in infants and children [15]. The major findings of the present study are that benzodiazepine receptors mediate aminophylline-induced convulsions and the anticonvulsant action of diazepam is diminished by pyrexia induced by Brewer's yeast in mice.

Adenosine is known to be an endogenous anticonvulsant in the brain [16]. This is supported by findings that stimulation of adenosine receptors exerts anticonvulsant activity in animal models of seizures and that adenosine receptor antagonists such as theophylline and caffeine are proconvulsant [17]. A number of studies have reported that the adenosine A1 receptor, but not the adenosine A2 receptor, reduces convulsions induced by kainic acid, bicuculline, penty-

lenetetrazol, chemical kindling and electroconvulsive shock [18–20]. However, a number of studies have reported that adenosine A1 receptor agonists fail to prevent [21–23] or to protect against theophylline-induced convulsions [24]. Based on these results, it has been suggested that theophylline-induced seizures are produced by mechanisms other than those involving the adenosinergic system [21]. In this study, neither the adenosine A1 receptor agonists (CCPA and CPA) nor the adenosine A2 receptor agonist CPCA had any effect on aminophylline-induced convulsions in ddY mice. On the other hand, theophylline has been reported to inhibit binding of GABA and diazepam to GABA_A receptors in brain membranes, although the affinities are low [25–26]. Therefore, it is possible that a high dose of theophylline would produce the convulsions via GABA_A and/or benzodiazepine receptors.

GABA is a major inhibitory neurotransmitter in the brain, whereas glutamic acid is an excitatory amino acid neurotransmitter. It is now widely accepted that the impairment of GABA neurotransmission by blockade of GABA_A receptors and the enhancement of glutamic acid neurotransmission by activation of NMDA may be the underlying factors in epilepsy [27]. Amabeoku [28] reported that theophylline (300 mg/kg, i.p.)-induced convulsions were suppressed by the selective GABA_A receptor agonist muscimol, the GABA_B receptor agonist baclofen, the GABA uptake inhibitor diamino-N-butyric acid (DABA), and the potent inhibitor of GABA transaminase amino-oxycetic acid (AOAA) in female albino mice. In addition, they found that the NMDA receptor antagonists, D-AP5 and ketamine, suppressed theophylline-induced convulsions [28]. However, other investigators have reported that the NMDA receptor antagonists, dizocilpine and ketamine, were ineffective in antagonizing the convulsions in male rats and mice, respectively [10, 23]. Thus, there may be strain differences in the effects of GABA receptor agonists and NMDA receptor antagonists against theophylline-induced convulsions. In this study, muscimol, baclofen and dizocilpine did not have any significant effect on the convulsions induced by aminophylline in male ddY mice.

Clinical data indicate that theophylline may induce repetitive generalized seizures in asthmatic patients, and antiepileptic drugs such as diazepam and pheno-

barbital, administered at high doses, can partially prevent the convulsions in such cases [29]. Previous studies have shown that diazepam and phenobarbital antagonize theophylline-induced convulsions in mice, but the remaining antiepileptics (acetazolamide, carbamazepine, diphenylhydantoin, ethosuximide, trimethadione) are ineffective in mice [10]. These findings indicate that theophylline-induced convulsions are relatively resistant to antiepileptic drugs. In the present study, diazepam dose-dependently prolonged the onset and significantly decreased the incidence of aminophylline-induced convulsions, in agreement with previous findings [10, 24, 27, 28]. Therefore, it is suggested that benzodiazepine receptors are involved in mediating the convulsant action of aminophylline.

In this study, Brewer's yeast increased the body temperature of mice, and also significantly shortened the onset and significantly increased the incidence of aminophylline-induced convulsions. Moreover, the ability of diazepam to ameliorate the aminophylline-induced convulsions was diminished by Brewer's yeast. These results indicate that benzodiazepine receptors are involved in the mechanism by which Brewer's yeast-induced pyrexia aggravates aminophylline-elicited convulsions.

It is well known that benzodiazepines are agonists for the GABA_A receptor complex, and facilitate inhibitory GABAergic neurotransmission via the enhancement of GABA-induced chloride conductance [5]. In the current study, the proconvulsant actions of GABA_A receptor antagonists, picrotoxin and pentylenetetrazol, were enhanced by Brewer's yeast. These findings suggest that GABA_A receptor are involved in the aggravation of the convulsions by Brewer's yeast-induced pyrexia. It has been reported that adenosine presynaptically reduces inhibitory GABA neurotransmission [30]. Thus, GABA_A receptors are presumed to be an important nervous system component involved in the aggravation of the theophylline-elicited convulsions by pyrexia. In addition, fever is a systemic response to infection, inflammation, or stress. Therefore, further studies will be necessary in order to clarify the precise mechanisms of the decreased convulsion threshold of theophylline in fever.

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