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Neuromodulatory Activity of Ethanolic Ginger Extract Versus Theophylline-Induced Seizures in Rats

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ABSTRACT

Objective: Seizures associated with theophylline toxicity carry a high morbidity and mortality.The present work aims at studying the effect of pretreatment of rats with ginger on the forebrain levels of the neurotransmitters glutamate and GABA in rats after induction of convulsions by theophylline.

Methods: The median convulsive dose (CD50), least convulsive dose and the achieved serum levels of theophylline, was determined either alone or after pretreatment with ginger. The forebrain levels of the neurotransmitters glutamate and GABA were measured in rats given theophylline, alone and after pretreatment with ginger extract.

Results: Ethanolic ginger extract in a dose of 200 mg 15 minutes before theophylline in a dose of 200 mg/kg produced significant protection against theophylline-induced seizures (produced 80% decrease in incidence of seizures). Ethanolic ginger extract pretreatment produced significant elevation of the median convulsive dose (CD50) of theophylline from 210 mg/kg to 235 mg/kg. Results have shown that cellular brain glutamate concentrations decreased significantly contrary to the significant increase in GABA levels ($P < 0.05$) in rats given ginger extract 5 minutes prior to 200 mg/kg theophylline compared with control group and theophylline-treated group.

Conclusions: The present work suggests a possible effect of ginger extract on GABA and glutamate neurotransmission that may have a protective role against theophylline-induced seizures.

KEYWORDS: Ginger, Neuromodulatory, Theophylline, Seizures

INTRODUCTION

Theophylline, a methylxanthine derivative which was widely used in the treatment of asthma and bronchopulmonary obstructive diseases, is known to produce seizures which might be due to non-selective antagonistic effect on central adenosine receptors[1]. Seizures associated with theophylline toxicity carry a high morbidity and mortality. The "typical" theophylline seizure is described as focal in onset, then generalized and is often refractory to pharmacologic intervention[2].The patient whose chronic use of theophylline is accompanied by intoxication is at risk for seizure at a much lower threshold. In this setting, chronologic age is the best predictor of CNS toxicity with infants and those over 60 years at highest risk[3].Chronic theophylline intoxication carries a greater risk of seizures than acute intoxication. Thus, acute overdoses rarely lead to seizures unless theophylline levels exceed 100 mg/L. In contrast chronically intoxicated patients may get seizures with levels below 60 mg/L[4-5].Most studies have reported using multiple drugs in an attempt to control the seizures[6]. Diazepam in conjunction with other drugs is generally considered effective, whereas phenytoin especially when used alone is not[4].

Glutamate is the major excitatory neurotransmitter in the human neocortex release as their primary neurotransmitter[7]. Enhanced glutamatergic activity is coupled tightly to increased cerebral energy metabolism[8].On the contrary, GABA is the major inhibitory neurotransmitter in the adult human cortex[7].

Ginger, the rhizome of Zingiber officinale, is used in many foods and beverages. It contains a number of active constituents. Ginger oil that comprises 1-3% of its weight contains a high percentage of hydrocarbons, mainlyzingiberene, bisapolene, and zingiberol[9-11]. Grant et al, reported that ginger is used in traditional medicine since thousands of years in many countries like China and India for relieve of some clinical conditions e.g. nausea, headache, cold sand rheumatic disorders[12]. It is used in China for cold extremities and after blood loss to resuscitate the patient[13].

Additionally, it is beneficial in treatment of gastric ulcers[14-15]. Stoilova et al. had reported that Zingiber officinale possesses an antioxidant activity[16]. More recent studies revealed that ginger has an anti-oxidative stress activity and neuroprotective effects that may be due to an influence on inhibitory and excitatory neurotransmitters, and calcium channel inhibition[17]. Vishwakarma and his colleagues suggested that the benzene fraction of a petroleum ether extract of dried rhizomes of ginger has anticonvulsant, anxiolytic and antiemetic activities[18].Mascolo et al. mentioned that gingerols have sedative and analgesic in vitro and in vivo[19].Many recent studies in literature had reported that ginger exhibits neuroprotective effects [20-21].

In the present work, the median convulsive dose (CD50), least convulsive dose and the achieved serum levels of theophylline, was determined either alone or after pretreatment with ethanolic extract of ginger. The present work investigates also the effect of pretreatment of rats with ginger on the forebrain levels of the neurotransmitters glutamate and GABA in rats after induction of convulsions by theophylline.

MATERIALS AND METHODS

Materials

Theophylline (ICN biomedicals, Inc) was soluble in warm saline. Ethanolic extract of Zingiber officinale solutions were freshly prepared.

Preparation of ethanolic extract of ginger

Smaller pieces of the Zingiber officinale rhizomes were dried under shade for 10-day duration and then pulverized by using a manual blenderto form a coarse powder. According to the method described by Giriraju and Yunus, 500grams of ginger were minced into fine pieces and then suspended in 1000 ml of 70% ethanol. The suspended minced ginger was continuously shacked for 48 hoursat constant intervals of time and then, by a sterile muslin cloth, undergone filtration so a residue of ginger and a filtrate were obtained. To obtain the ethanolic extract, the filtrate was placed over steam bath apparatus for 5 days so that enhancing evaporation of ethanol content from the filtrate. The dried extract was obtained after 5 days and then, by using a mortar and pestle, was pulverized into fine powder[22]. Ten grams of ethanolic ginger extract powder was then dissolved in 100 ml of dimethyl sulphoxide (DMSO) to obtain 10% ethanolic ginger extract stock solution.

Animals

Adult male rats weighing 150-200g were used. The animals were group housed in plastic cages and maintained under standard laboratory conditions with a natural light-dark cycle. Rats were left to acclimatize to the environment for at least a week before the experiments. Food and water were allowed ad libitum. The experimental protocol wasapproved by the Animal Ethical Committee inaccordance with the guide for the care and use oflaboratory animals prepared by National Institutes of Health (NIH).

Determination of the marginal dose of theophylline that elicits convulsions i.e. the least convulsive dose:

5 groups of rats each was comprised of 5 animals.

Treatment schedules:

Group A: was given theophylline i.p in a dose of 50 mg/kg (i.e. ½ the therapeutic dose).

Group B: was given theophylline i.p in a dose of 100 mg/kg (i.e equivalent to the therapeutic dose in human).

Group C: was given theophylline i.p in a dose of 200 mg/kg (double the therapeutic dose).

Group D: was given theophylline i.p in a dose equals double the dose given to the group C.

Group E: was given a dose of theophylline i.p equals double the dose given to group D.

The doses of theophylline given to rats were selected after calculation of the equivalent dose to that of the therapeutic dose of theophylline given to humans in cases of bronchial asthma i.e. 14-16 mg/kg/day[23].

Measurement of serum level of theophylline at the least convulsive dose

A group of male rats weighing 150-200 gm. comprised of 10 animals was given theophylline at the least dose eliciting convulsions as previously determined. Samples of blood of the convulsing rats were taken, and then centrifuged to extract the serum. The level of theophylline in each sample of serum was measured by fluorescence polarization immunoassay (FPIA)[24].

Calculation of the Median Convulsive Dose (CD50) of theophylline in rats

Computation of the median convulsive dose and its 95% confidence limits for theophylline were proceeded according to the method of Litchfield and Wilcoxon[25]. Groups of 10 rats were injected with graded doses of theophylline. Percentage incidence of seizures in each group was determined during a period of 30 minutes after theophylline administration.

Effect of ginger extract pretreatment on theophylline induced seizures and CD50 of theophylline in rats:

6 groups of rats each was comprised of 10 animals

Group A: was given theophylline i.p in a dose of 200 mg/kg.

Group B: was given i.p 0.5 ml of 8% ethanol, 5 minutes before theophylline i.p in a dose of 200 mg/kg.

Group C: was given ethanolic ginger extract i.p in a dose of 10 mg/kg15 minutes before theophylline i.p in a dose of 200 mg/kg.

Group D: was given ethanolic ginger extract i.p in a dose of 50 mg/kg15 minutes before theophylline i.p in a dose of 200 mg/kg.

Group E: was given ethanolic ginger extract i.p in a dose of 100 mg/kg15 minutes before theophylline i.p in a dose of 200 mg/kg

Group F: was given ethanolic ginger extract i.p in a dose of 200 mg/kg15 minutes before theophylline i.p in a dose of 200 mg/kg

Effect of ethanolic ginger pretreatment on CD50 of theophylline:

Groups of 10 rats were injected i.p with graded doses of theophylline 60 minutes after their pretreatment with ethanolic ginger extract injected i.p in a dose of 200 mg/kg. Percentage incidence of seizures in each group was determined during a period of 30 minutes after theophylline administration. Computation of the median convulsive dose (CD50) and its 95% confidence limits for theophylline were proceeded according to the method of Litchfield and Wilcoxon[25].

Measurement of Glutamate and GABA levels in rat forebrain

Animal protocol

Glutamate and GABA levels in forebrains of the following groups of rats were measured:

1. Control normal rats weighing 150-200g (negative group) comprised of 5 animals
2. Positive control group challenged with theophylline in the least convulsive dose
3. Rats given ethanolic ginger extract i.p in a dose of 200 mg/kg15 minutes prior to theophylline in the least convulsive dose
4. Rats given ethanolic ginger extract i.p in a dose of 200 mg/kg15 minutes prior to theophylline in the least convulsive dose
5. Rats given ethanolic ginger extract i.p in a dose of 200 mg/kg15 minutes prior to theophylline in the least convulsive dose

Rat forebrain extraction

According to the method described by Laura and Ognen, rats were decapitated and brains were quickly removed (<90 seconds) rostral to the cerebellum and frozen in liquid nitrogen. Frozen brains were extracted in 3.5 ml cold 12% perchloric acid (PCA) stock solution containing 7.7 mM dichloracetic acid (Sigma) and centrifuged at 3200×g for 15 minutes at 4 °C. The neutral supernatant was centrifuged at 3200×g for 10 minutes at 4 °C. 0.5 g chelating resin (Sigma) was added to the neutral solution which is then filtered, and lyophilised. The dried powder was dissolved in neutral 50 mM deuterated phosphate in D2O containing 2 mM isopropanol[26].

Statistical analysis of the results:

CD50 values and analysis of the results obtained in the convulsive tests were calculated by fitting the data by linear regression analysis as described by Litchfield and Wilcoxon[25]. Significance tests of CD50 values of theophylline, alone and after pretreatment with Ginger extract in rats were determined by using 95% confidence limits according to Snedecor[27]. The significance of the differences was determined using the student's t-test. The difference was regarded as significant when $P < 0.05$ and as a highly significant when $P < 0.01$[27].

RESULTS

Determination of the marginal dose of theophylline that elicits convulsions i.e. the least convulsive dose (Fig.1)

Group A (50 mg/kg): No neurological manifestations.

Group B (100 mg/kg): No neurological manifestations were observed.

Group C (200 mg/kg): one animal showed focal clonic seizures in hind limb after a latency of about 10 minutes. These seizures continued for less than 30 seconds. The other 4 animals showed restlessness and tremors.

Group D (400 mg/kg): one animal showed generalized tonic-clonic seizures 3 minutes after injection of theophylline and continued for few seconds then died. The other 4 rats showed generalized tonic-clonic convulsions after a latency of 5 – 10 minutes for about 20 seconds and then died.

Group E (800 mg/kg): Generalized tonic-clonic seizures of few seconds after about 1 minute of theophylline administration.

So, in view of these observations, theophylline in a dose of 200 mg/kg is considered the least convulsive dose in rats. This dose is equivalent to double the therapeutic dose of theophylline, in bronchial asthma, in human. In this study, this dose was used after treating rats with adenosine and its agonists in the following steps.

Measurement of serum level of theophylline at the least convulsive dose:

It was observed that serum level of theophylline in convulsing rats was variable and above 20 μg/ml (normal therapeutic range). Convulsions occurred in 4 out of 10 rats. Serum levels of theophylline were 72, 55, 47 and 39 μg/ml.

Calculation of CD50 of theophylline in rats:

The median convulsive dose (CD50) of theophylline injected intraperitoneally into rats was equivalent to 210 (188.34 – 234.15) mg/kg.

Total animals = 50

Number of doses = 5

Animals/doses = 50/5 = 10

$(Chi)^2 = 0.488 \times 10 = 4.88$

Degrees of freedom = 3

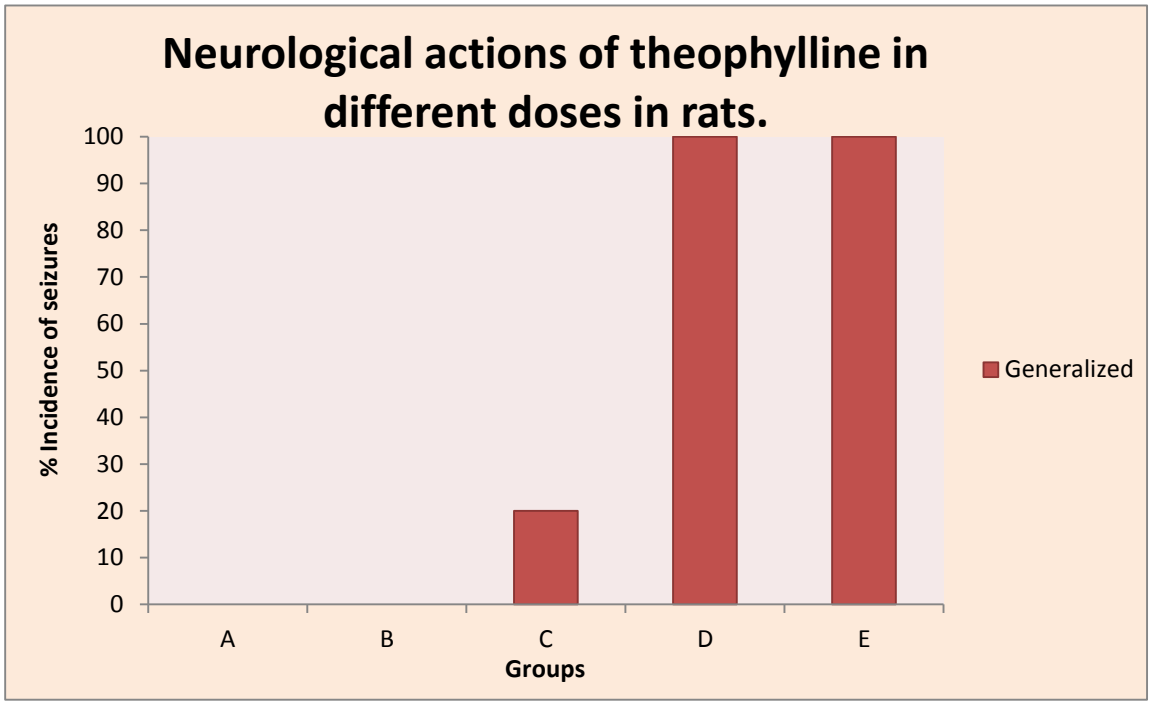
Tabulated $(Chi)^2$ for n of 3 = 7.82 (see table 4)

.. $(Chi)^2$ calculated is less than $(Chi)^2$ tabulated
∴The data are not significantly heterogenous
CD_{84} = 260 mg/kg
CD_{50} = 210 mg/kg
CD_{16} = 170 mg/kg

$$S = \frac{260/210 + 210/170}{2} = \frac{1.24 + 1.235}{2} = 1.24$$

N = 30
Exponent = $2.77/\sqrt{30}$ = 2.77/5.47 = 0.51
$FCD_{50} = 1.24^{0.51} = 1.115$
CD_{50} X FCD_{50} = 234.15
CD_{50}/FCD_{50} = 188.34
∴CD_{50} and its 95% confidence limits = 210 (188.34–234.15) mg/kg

Fig 1: Determination of the marginal dose of theophylline that elicits convulsions



A = theophylline 50 mg/kg, B = 100 mg/kg, C = 200 mg/kg, D = 400 mg/kg, E = 800 mg/kg.

Table 1: CD50 and its 95% confidence limits of theophylline injected intraperitoneally in rats.

Dose (mg/kg)	Convulsed Tested	Observed % convulsed	Expected % convulsed	Observed expected	Contribution to $(Chi)^2$
100	0/10	Zero	0.02	0.02	0.0000
150	2/10	20	5	15	0.4600
200	4/10	40	40	0	0.0000
250	8/10	80	80	0	0.0000
300	10/10	98.4	95	3.4	0.0280
				Total	**0.488**

Total animals = 50
Number of doses = 5
Animals/doses = 50/5 = 10
$(Chi)^2$ = 0.488 X 10 = 4.88
Degrees of freedom = 3
Tabulated $(Chi)^2$ for n of 3 = 7.82(see table 4)
.. $(Chi)^2$ calculated is less than $(Chi)^2$ tabulated
∴The data are not significantly heterogenous
CD_{84} = 260 mg/kg
CD_{50} = 210 mg/kg
CD_{16} = 170 mg/kg

$$S = \frac{260/210 + 210/170}{2} = \frac{1.24 + 1.235}{2} = 1.24$$

N = 30
Exponent = $2.77/\sqrt{30}$ = 2.77/5.47 = 0.51
$FCD_{50} = 1.24^{0.51} = 1.115$
CD_{50} X FCD_{50} = 234.15
CD_{50}/FCD_{50} = 188.34
∴CD_{50} and its 95% confidence limits = 210 (188.34–234.15) mg/kg

Effect of ginger extract pretreatment on theophylline-induced seizures in rats

Group A (Theophylline 200 mg/kg) and **Group B** (8% ethanol before theophylline 200 mg/kg):
After a latency of about 10 minutes, 4 animals exhibited tremors and generalized clonic convulsions for about 30

seconds. The other animals showed restlessness and marked activity with frequent tremors.

Group C (10mg ethanolic ginger extract 15 minutes before theophylline 200 mg/kg):

After a latency of about 10 minutes, 3 animals showed tremors followed by generalized clonic convulsions for about a minute. The other animals exhibited restlessness and intermittent tremors without convulsions.

Group D (50mg ethanolic ginger extract 15 minutes before theophylline 200 mg/kg):

Generalized tremors and frequent clonic convulsions of for about half a minute, after a latency of 5-10 minutes, happened in two rats with tremors and restlessness of the other animals.

Group E (100mg ethanolic ginger extract15 minutes before theophylline 200 mg/kg):

Generalized clonic seizures occurred in one animal after a latency of 15 minutes and continued for about 15 seconds.Fewer tremors were observed in other animals.

Group F (200mg ethanolic ginger extract15 minutes before theophylline 200 mg/kg):

Generalized clonic convulsions were observed in only one rat after a latency of 30 minutes and continued for few seconds. No tremors or restlessness in the others.

Dose	Convulsed ---	Observed	Expected	Observed -	Contribution to
(mg/kg)	tested	% convulsed	% convulsed	expected	$(Chi)^2$
100	0/10	0.5	0.15	0.35	0.0080
150	1/10	10	6	4	0.0280
200	3/10	30	30	0	0.0000
250	6/10	60	60	0	0.0000
300	8/10	80	80	0	0.0000
350	10/10	97.1	91	6.1	0.0500
				Total	**0.086**

Table 2: CD50 and its 95% confidence limits of theophylline after ginger pretreatment.

The median convulsive dose (CD50) of theophylline injected i.p into rats 5 minutes after adenosine was equivalent to 235 (202.6 – 272.6) mg/kg.

Total animals = 60

Number of doses = 6

Animals/doses = 60/6 = 10

$(Chi)^2$ = 0.086 X 10 = 0.86

Degrees of freedom = 4

Tabulated $(Chi)^2$ for n of 4 = 9.49 (See table 4)

.. $(Chi)^2$ calculated is less than $(Chi)^2$ tabulated

∴The data are not significantly heterogenous

CD_{84} = 310 mg/kg

CD_{50} = 235 mg/kg

CD_{16} = 175 mg/kg

$$S = \frac{310/235 + 235/175}{2} = \frac{1.32 + 1.34}{2} = 1.33$$

$\overline{N}$ = 30

Exponent = $2.77/\sqrt{30}$ = 0.51

$FCD_{50} = 1.33^{0.51} = 1.16$

CD_{50} X FCD_{50} = 272.6

CD_{50}/FCD_{50} = 202.6

∴CD50 and its 95% confidence limits = 235 (202.6 – 272.6) mg/kg

As shown in table 3, cellular brain glutamate concentrations decreased significantly contrary to the significant increase in GABA levels (P < 0.05) in rats given ethanolic ginger extract i.p in doses of 200 mg 15 minutes prior to theophylline in the least convulsive dose compared with control group and theophylline-treated group.

Table 3: Glutamate and GABA levels in rat forebrain

Group	Glutamate	GABA
Negative control	12.5 ± 0.3	2.28 ± 0.05
Theophylline in the least convulsive dose	14.25 ± 0.2*	1.75 ± 0.03*
Ginger extract i.p in a dose of 50mg 5 minutes prior to theophylline in the least convulsive dose	10.2 ± 0.1*#	2.54 ± 0.01*#
Ginger extract i.p in a dose of 100mg 5 minutes prior to theophylline in the least convulsive dose	10.7 ± 0.2*#	2.38 ± 0.03*#
Ginger extract i.p in a dose of 200mg 5 minutes prior to theophylline in the least convulsive dose	11.2 ± 0.1*#	2.42 ± 0.03*#

Values represent the mean concentrations (mM) with ± SEM.*P <0.05 versus control using.#P <0.05 versus theophylline, in the least convulsive dose.

Table (4): Values of t and $(chi)^2$ for P = 0.05

Degree of freedom	t	$(chi)^2$
1	12.70	3.48
2	4.30	5.99
3	3.18	7.82
4	2.78	9.49
5	2.57	11.10
6	2.45	12.60
7	2.36	14.10
8	2.31	15.50
9	2.26	16.90
10	2.23	18.30

DISCUSSION

Theophylline is a methylxanthine derivative which is widely used in the treatment of asthma and bronchopulmonary obstructive diseases. It has a low therapeutic safety margin and serum concentrations above the therapeutic concentrations are usually associated with toxicity. Neurological symptoms of toxicity include agitation, tremors and seizures which may be generalized or focal with secondary generalization[28]. Postulated mechanisms have included both cerebral vasoconstriction (related to adenosine blockade) and rises in cerebral concentrations of cyclic AMP which have been shown to be epileptogenic in rats[29]. The treatment of theophylline-induced seizures is rather a difficult task. No established treatment protocol exists, in theophylline overdose[4]. Conventional antiepileptic drugs very poorly control this type of convulsions and are practically ineffective in lowering the mortality[30]. These facts have tempted us to carry out the present work in order to evaluate the effect of pretreatment with ginger extract on theophylline-induced seizures.

Ethanolic ginger extract in a dose of 200 mg 5 minutes before theophylline in a dose of 200 mg/kg produced significant protection against theophylline-induced seizures (produced 80% decrease in incidence of seizures). Ethanolic Ginger extract pretreatment produced significant elevation of the median convulsive dose (CD50) of theophylline from 210 mg/kg to 235 mg/kg.

Previous studies reported that neuroprotective effect of ginger is not fully explained. The present study illustrates how administrations of ethanolic ginger extract prior to induction of convulsions by theophylline; alter the cellular brain levels of both the major excitatory neurotransmitter glutamate and the major inhibitory neurotransmitter GABA. Results have shown that cellular brain glutamate concentrations decreased significantly contrary to the significant decrease in GABA levels ($P < 0.05$) in rats given ginger extract 15 minutes prior to 200 mg/kg theophylline compared with control group and theophylline-treated group.

Based on the results obtained in the present study, it seems that ginger may have a protective effect against theophylline-induced convulsions via enhancing inhibitory GABA neurotransmission and blocking excitatory glutamate neurotransmission.

Fewer studies agree that ginger increases GABA in some brain areas e.g. Hoda and Elham, 2011 reported that ginger supplementation showed increased GABA and other amino acids in the hippocampus and cortex in senile female rats[31]. A study by Waggas observed that ginger extract has a neuroprotective effect against monosodium glutamate toxicity[32]. It may be owed to its anti-oxidant activities[21]. Sharma and Singh observed that ginger juice increases the antioxidant enzymes; glutathione peroxidase, superoxide dismutase and catalase and decrease lipid peroxidation[33].

CONCLUSION

A possible effect of ginger extract on GABA and glutamate neurotransmission may have a protective role against theophylline-induced seizures. Further animal and human studies are needed in near future to prove the neuromodulatory and neuroprotective effects of ginger in epileptic disorders.

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