Neurophysiological Studies on the Effect of Acetone on Pentylenetetrazole-Induced Seizure in Rats

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ABSTRACT

Recent interest in the anticonvulsant effects of acetone has stemmed from studies related to the ketogenic diet (KD). Despite knowledge of acetone's anticonvulsant properties, the neurochemical basis for this effect is not well known. The present study aimed to explore the neurochemical basis underlying the anticonvulsant effect of acetone in pentylenetetrazol (PTZ) - induced convulsions. This was achieved through determining the neurochemical changes of acetone in pentylenetetrazol (PTZ) – treated rats. Male adult rats received either saline, acetone (15 m mol/kg i.p.), PTZ (60 mg/kg, i.p.), or acetone 3 h before PTZ injection. Result showed that the maximum concentration of acetone reached about 3 h after acetone administration. Thus, the animals were administered pentylentetrazole three hours after acetone treatment. Pentylenetetrazole treated rats exhibited epilepsy, increased brain levels of excitatory amino acids (glutamate and aspartic acids) and decreased levels of inhibitory amino acid (γ-aminobutyric acid and glycine). In addition, pentylenetetrazole treatment decreased total antioxidant activity and reduced glutathione (GSH) in brain. Acetone pretreatment remarkably decreased seizure incidence rate and increased seizure latency. Moreover, acetone significantly minimized the disturbing effect of pentylenetetrazole on the redox status and the balance between excitatory and inhibitory amino acids. The study indicated that the epilepsy might be mediated, at least partially, through the disturbance in the redox status and imbalance between excitatory and inhibitory amino acids in the brain. Moreover, the study indicated that the antiepileptic effect of acetone might be due to its antioxidant effect and sustaining the balance between excitatory and inhibitory amino acids. Moreover, the study might recommend the concurrent intake of ketogenic diets with the conventional antiepileptic drugs. In addition, synthesizing new chemical entities yielding acetone during its metabolism in the body might provide new candidates as antiepileptic drugs.

INTRODUCTION

Epilepsy is considered one of the most common neurological disorders worldwide, with a prevalence of 0.5-1% in the general population[(1)]. Epilepsy continues to be a disease awaiting safer drugs with improved antiepileptic effectiveness. Moreover, combinations of conventional antiepileptic drugs (AEDs) might fail to effectively control seizures[(2)]. Consistently, about 30% of epileptic patients do not respond to clinically

established AEDs[3]. The neurobiological relationships between epilepsy and affective disorders are receiving increased attention[4,5]. Epilepsy is a neurological disorder characterized by spontaneous, recurrent and paroxysmal cerebral discharge leading to persistent alterations in function and morphology of neurons[6]. The burst firing associated with prolonged epileptic discharges could lead to a large number of changes and cascades of events at the cellular level. These effects include activation of glutamate receptors, changes in composition of glutamate and γ-aminobutyric acid (GABA) receptors, cytokine activation and oxidative stress, modulation in neurogenesis and neuroplasticity or activation of some late cell death pathways[1,7,8]. Consistently, N-methyl-D-aspartate (NMDA) receptor antagonists were shown to possess anticonvulsant properties against several insults including pentylenetetrazole (PTZ)-induced seizures and to enhance the effects of AEDs [9,10].

Despite progress in current antiepileptic therapy, neither are seizures adequately controlled nor medications free of untoward side effects[11]. On the other hand, a ketogenic diet has been used successfully to treat patients with intractable epilepsy[12]. In addition, many studies on the anticonvulsant effects of a ketogenic diet have been performed, however, the mechanism remains unknown[13,14]. Several hypotheses have been proposed to explain the anticonvulsant effects of a ketogenic diet.[15], such as the alterations in energy metabolism in the brain with a ketogenic diet intake[16]. The ketone bodies, b-hydroxybutylate, acetoacetate and acetone are significantly increased in the plasma of patients receiving a ketogenic diet[17]. Among these three ketone bodies, acetoacetate and acetone easily pass through the blood brain barrier, and partly replace glucose as fuel in the brain[18], leading to the changes in energy metabolism in the brain[14,18]. These changes might be related to the anticonvulsive effect associated with a ketogenic diet in animal models of neurodegenerative diseases. Acetone is the principal ketone body elevated in the ketogenic diet (KD), with demonstrated robust anticonvulsant properties across a variety of seizure tests and models of epilepsy[19]. In addition, the anticonvulsant effects of acetone have been reported in various animal models of epilepsy [19, 20].

The present study was conducted to explore the neurochemical basis underlying the antiepileptic effect of acetone in rats. This was achieved through determining the effect of acetone on the brain content of the excitatory (glutamate and aspartic) and inhibitory (GABA and glycine) amino acids and the redox status (total antioxidant activity and reduced glutathione).

MATERILAS & METHODS

Experimental animals: male adult Sprague Dawley rats (150-200 g) were kindly provided from our breeding center at NODCAR and kept for a week for acclimatization under normal conditions and constant temperature (25±1C°) with *ad libitum*

water and food until starting the experiment.

***Chemicals*:** All chemicals, unless specified other-wise, were purchased form Sigma-Aldrich Chemical Co. (St. Louis, MO).

Drug: Pentylenetetrazole was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO).

A total number of forty rats with an average weight of 175g, were administered an i.p. dose of acetone (15 mmol/kg) and blood samples were taken at time intervals 1, 2, 3, 5 and 10 h to asses the time corresponding to the highest concentration of acetone. The rats were decapitated and trunk blood was collected in 1 ml heparinized tubes. The heparinized samples were centrifuged at 3,000 rpm for 20 min at 4°C. Plasma was aspirated from the centrifuged specimen using a transfer pipette. Plasma samples were used to determine acetone.

In addition, a total number of thirty two rats were divided into four groups, group I received saline and served as control. Group II received single intraperitoneal injection of PTZ in convulsive dose of 60 mg/kg[21]. Group III was injected intraperitoneally with acetone (ACET, 15 mmol/kg). Group IV was injected intraperitoneally PTZ, 3h following acetone injection. After PTZ injection, rats were placed singly in plexiglass cages and were observed for 30 min. Incidences and latency of clonic convulsive attacks, which lasts over 3 s with an accompanying loss of righting reflex were recorded. Seizure latency for rats showing no convulsive attacks within the observation period was taken as 30 min[21]. Rats were euthanized by decapitation after seizures assessment; brains were removed and dissected bilaterally. One brain half was homogenized in 75% (v/v) aqueous methanol (HPLC grade, Sigma-Aldrich, MO, USA), homogenates were centrifuged at 4000×g, 20 min, 4 °C, and supernatants were employed for the determination of brain amino acids contents. The second brain half was homogenized in ice cold saline and was used for the estimation of brain redox status (total antioxidant activity and reduced glutathione).

Methods:

Level of acetone in plasma was determined by HPLC method according to Brega *et al.*[22]. Free amino acids were determined using precolumn derivatization HPLC-UV method[23]. Total antioxidant activity was determined using the colourimetric method of Blois[24]. Reduced glutathione was determined by HPLC method according to Jayatilleke and Shaw [25].

Statistical Analysis.

Data presented as means ± SE. One-way ANOVA followed by LSD test were used to evaluate significant differences from the control group. $P< 0.05$ was considered to be statistically significant. Statistical processor system support (SPSS) for Windows software, release 10.0 (SPSS, Inc, Chicago, IL) was used.

RESULT

As shown in Figure 1. the maximum concentration of acetone attained after 3h of acetone administration to give 800.0 ± 95.5

mg/L and gradually declined to give 100 .8 ± 35 mg/L after 10 h.

Table 1 depicts that PTZ- treated rats exhibited clonic convulsions with 3.5-min average seizure latency. Acetone pretreatment significantly decreased the convulsions' incidence and prolonged seizure latency.

Data in table 2 shows that PTZ significantly (P <0.05) reduced brain GABA and glycine contents and increased glutamate and aspartate contents compared to control group (Table 2). Acetone treatment significantly increased GABA and decreased glutamate content. Acetone pretreatment remarkably prevented the disturbing effect of PTZ on the free amino acid levels

(Table 2). Data in tables 3 shows that pentylenetetrazole treatment significantly decreased both total antioxidant activity and GSH content in rat brain. Acetone treatment significantly (P <0.05) increased both total antioxidant activity and GSH content in rat brain. Acetone pretreatment significantly minimized the PTZ- adverse effect on the total antioxidant activity and GSH content.

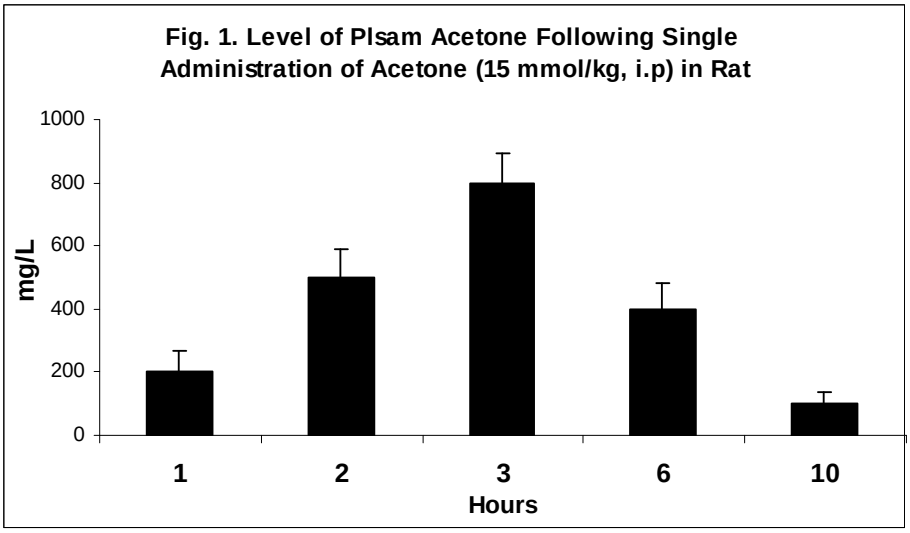

Table 1. Effect of Acetone (ACET, 15 mmol/kg, p.i.) on Pentylenetetrazole (PTZ-induced Clonic Seizures in Rats

Groups	Clonic Seizures Incidence (%)	Clonic Seizure Latency (min.)
PTZ	100	3.51 ± 0.55
ACET + PTZ	70	15.12 ± 1.38 *

*Data are expressed as means ±SEM; *P<0.05 significant different from control (n=8)*

Table 2. Effect of Acetone (ACET, 15 mmol/kg, i.p.), Pentylenetetrazole (PTZ, 60 mg/kg, p.i.) alone or in combination on Levels of Amino Acids Levels (µmol/g tissue) in Rat Brain

Groups	Brain Amino Acids Contents (µmol/g Tissue)			
	Aspartic acid	**Glutamic acid**	**GABA**	**Glycine**
CONTOL	5.52 ± 0.37	6.95 ± 0.24	3.40 ± 0.14	2.17 ± 0.08
PTZ	6.37 ± 0.14 *	8.20 ± 0.16 *	2.20 ± 0.10 *	1.83 ± 0.04 *
ACET	4.95 ± 0.28 +	6.25 ± 0.32 *, +	3.88 ± 0.10 *, +	2.33 ± 0.09 +
ACET + PTZ	5.32 ± 0.15 +	7.35 ± 0.16 +	3.10 ± 0.09 +	2.28 ± 0.05 +

Data are expressed as means ±SEM; P<0.05 significant different, (n=8)
** Significant different from control*
+ significant different from PTZ group

Table 3. Effect of Acetone (ACET, 15 mmol/kg, i.p.), Pentylenetetrazole (PTZ, 60 mg/kg, p.i.) alone or in combination on Total Antioxidant Activity and Content of Reduced Glutathione in Rat Brain

Group	Total antioxidant	Reduced glutathione
Control	57.39 ± 1.04	1.65 ± 0.07
PTZ	32.85 ± 1.88 *	1.29 ± 0.04 *
ACET	54.78 ± 2.45 +	1.63 ± 0.04 +
ACET+ PTZ	59.71 ± 2.74 +	1.59 ± 0.10 +

*Data are expressed as means ±SEM; *P< 0.05 significant different, (n=8)*
** Significant different from control*
+ Significant different from PTZ group

DISCUSSION

The present data showed that acetone required from 2-3 h to reach the maximum concentration in the blood. It is important to note that the time required for the drug to reach the maximum level in the blood is dependent on the route of administration and the metabolic status which determines the rate of drug's biotransformation and clearance. Consistently, a previous study indicated that acetone takes about 2 hours to reach the maximum level after intravenous administration[26].

In addition, the convulsive effect of PTZ might be due to the activation of the excitatory neurotransmission through the excitatory amino acids (aspartic and glutamic) and/ or by suppressing the inhibitory neurotransmission by inhibitory amino acids (GABA and glycine). In the present study, the increase in glutamate and the decrease in GABA contents might be due to the inhibition of the enzymatic activity of GABA synthesizing enzyme glutamic acid decarboxylase (GAD) and/or the decrease in GAD protein levels. Consistently, a recent study reported that antibodies to GAD are found at

high levels with low GABA concentration in a subgroup of patients with chronic epilepsy[27], indicating a role for immune-mediated enzyme destruction and GABAergic dysfunction.

In accordance to this interpretation, a previous study indicated that both excitatory and inhibitory amino acids are involved in epilepsy and that glutamatergic activation is responsible for the persistent down-regulation of postsynaptic GABA (A) receptors and erosion of synaptic inhibition[28]. Furthermore, GABAergic neurons exposed to glutamate *in vitro* showed a reduced dendrite growth and altered glutamic acid decarboxylase (GAD) 65- and 67-kDa isoform protein expression from mouse cortical GABAergic neurons [29,30]. Moreover, intraventricular microinjection of NMDA induced behavioral seizures and motor disorders[31]. It is worthy to note that glutamate and GABA are the most abundant neurotransmitters in the central nervous system, especially in the cerebral cortex, the site where thinking occurs and different sensations are interpreted and integrated.

Notably, seizure disorders are all related to low GABA activity which regulates the transmission of nerve impulses from one neuron to another. Thus, with the inhibited GABAergic neurotransmission, nerve cells fire too often and too easily. Hence, it is likely that the antiepileptic effect of acetone probably is due to the depressive effect of acetone on the excitatory neurotransmission. In accordance, previous studies indicated that ketogenic diet increased cerebrospinal fluid GABA content and increased brain synaptosomal GABA content[16,32]. A recent study of 5-month-old rats of the GAERS (genetic absence epilepsy rats of Strasbourg) strain showed that ketogenic diet decreased cortical glutamate levels using ^{13}C nuclear magnetic resonance spectroscopy[33]. Moreover, ketogenic diet has been reported to reduce aspartate level in brain regions, induces alterations in the metabolism of excitatory amino acids, with greater effects on aspartate than on glutamate[13,16]. In the present study, the observation that acetone pretreatment restored the normal levels and the balance between the excitatory and inhibitory neurotransmission in PTZ treated rats, whereas acetone alone depressed the levels of excitatory amino acids in normal rats might indicate a depressive effect of acetone. Moreover, it seems that the antiepileptic effect of acetone is not dependent on its metabolites, because acetone freely crosses blood–brain barrier, and its concentrations in blood and cerebrospinal fluid are similar in rats[34], whereas its metabolites seemingly can not cross biological membranes [14].

In addition, oxidative stress is one of possible mechanisms in the pathogenesis of epilepsy. It is interpreted that oxidative stress resulting from mitochondrial dysfunction gradually disrupts the intracellular calcium homeostasis, which modulates neuronal excitability and synaptic transmission making neurons more vulnerable to additional stress, and leads to neuronal loss in epilepsy[6]. In addition, the high

oxidative status is associated with the severity and recurrence of epileptic seizure. Hence, treatment with antioxidants is critically important in epileptic patients through scavenging the excessive free radicals to protect against the neuronal loss[6,35]. The observation that acetone pretreatment significantly attenuated the pro-oxidant effect of PTZ treatment might be attributed to acetone's antioxidant effect.

In accordance to our result, a previous study indicated that acetone was found to be active in animal models of tonic-clonic seizures, typical absence seizures, complex partial seizures, and atypical absence seizures associated with Lennox-Gastaut syndrome where the therapeutic indices are either comparable or better than that of valproate[17]. Mitochondrial dysfunction and oxidative stress has been suggested to play a role in the acute consequences of injuries that are known to provoke chronic epilepsy and their involvement in the chronic stages of acquired epilepsy[1,35]. In accordance, ketogenic diet has caused an elevation in glutathione peroxidase activity in rat hippocampus[36], and increased mitochondrial uncoupling protein levels and activity – which decreased reactive oxygen species (ROS) production[37]. In addition, ketone bodies provided a protective effect against oxidative stress in neocortical neurons by decreasing mitochondrial ROS production[38], and prevented oxidative stress cytotoxicity induced by H_2O_2 formed by glucose/glucose oxidase[39,40]. On the other hand, a recent study indicated that a high dose of acetone (7.0 gm/kg) induced oxidative stress leading to disturbance of the biochemical and physiological functions[41], which might indicate that the beneficial effect of acetone is a dose dependent.

The study concluded that epilepsy might be due to the imbalance between excitatory and inhibitory neurotransmission and oxidative stress. Acetone offered an antiepileptic effect probably due to its restorative effect of the balance between excitatory and inhibitory neurotransmission and its antioxidant effect. In addition, the study might encourage the concurrent intake of ketogenic diets with the conventional antiepileptic drugs. In addition, the study recommends the synthesis of new chemical entities yielding acetone during its metabolism in the body to be antiepileptic drugs candidates.

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دراسات فسيولوجية عصبية عن تأثير الأسيتون في الصرع المستحدث بمادة بنتيلينتترازول في الجرذان

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نشأ حديثا الاهتمام بتأثير الاسيتون المضاد للصرع و ذلك من خلال الدراسات الخاصة بالنظام الغذائي الكيتوني. على الرغم من معرفة خصائص الأسيتون المضادة للصرع معروفة جيدا الا أن الألية الكيميائية العصبية لهذا التأثير غير معلومة بصورة كاملة.

تهدف الدراسة الى اكتشاف التغيرات الكيميائية العصبية الكامنة وراء تأثير الاسيتون المضاد للصرع الناتج من عقار بنتيلينتترازول في ذكور الجرذان البالغة. تم حقن الجرذان بعقار بنتيلينتترازول بتركيز ٦٠ مجم/كجم في التجويف البريتوني. و حقن الاسيتون بتركيز ١٥ مللي مول/كجم. أظهرت النتائج أن أقصى تركيز للاسيتون في الدم يكون بعد ثلاث ساعات من الحقن. تم ظهور أعراض الصرع في الجرذان بعد ثلاث دقائق من حقن عقار بنتيلينتترازول .وتسبب حقن العقارفي زيادة مستوى الاحماض الامينية المثيرة (Glutamic and aspartic acids) و نقص في محتوى الاحماض الامينية المثبطة

(GABA and glycine) و نقص النشاط الكلي المضاد للاجهاد التأكسدي و كذلك نقص محتوي الجلوتاثيون المختزل.

أدى الحقن المسبق بالاسيتون الي تأخير حدوث نوبات الصرع وتقليل معدل حدوثها. كما منع الاسيتون تأثير عقار بنتيلينتترازول علي مستوى الاحماض الامينية المثيرة و المثبطة و منع حدوث الاجهاد التأكسدي.

تشيرالدراسة الى أن حدوث الصرع قد يكون من خلال نخفاض النشاط المضاد للأكسدة في المخ و انعدام التوازن بين الأحماض الأمينية المثيرة و المثبطة في المخ. كما تشير الدراسة الى ان تأثير الاسيتون المضاد للصرع قد يكون بسبب تأثيره المضادة للأكسدة وتأثير الحافظ للتوازن بين الأحماض الأمينية المثيرة و المثبطة. وبالإضافة إلى ذلك ، تؤيد الدراسة تناول الوجبات الغذائية الكيتونية مع العقاقير التقليدية المضادة للصرع. وبالإضافة إلى ذلك توصي بتخليق عقاقير تنتج الأسيتون من خلال عملية التمثيل الغذائي في الجسم لتكون أدوية مضادة للصرع.