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Involvement of GABA-ergic Transmission in the Anticonvulsant Effect of Ginkgo Biloba against Kainic Acid-induced Seizures in Mice

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Abstract *Ginkgo biloba* (GbE) is an herbal product that has been proven to be effective in many neurological disorders. However, its anticonvulsant activity is not sufficiently studied. The aim of this work is to study the anticonvulsant activity of GbE and the role of GABA-ergic transmission in this effect. Methods: (1) Studying the anticonvulsant activity of GbE in different dose levels (20, 30 and 50 mg/kg/d, orally) for 15 days against kainic acid (KA)-induced seizures in mice. (2) Measurement of the brain glutamate and GABA levels and glutamate decarboxylase (GAD) activity. Results: GbE showed a protective effect for animals against KA-induced seizures in a dose-related manner. This appeared in form of a significant increase in time of seizure onset and decrease in percent of seizures and mortality in animals treated with GbE. Furthermore, there was a significant decrease in brain glutamate level and increase in GABA level and GAD activity in GbE-treated groups relative to KA-treated group. Conclusion: From the obtained results, we can conclude that GbE has effective anticonvulsant activity against KA-induced seizures. This effect may be mediated via various mechanisms but GABA-ergic transmission plays a vital role in this effect. Future research directions include further studies of the other possible mechanisms of GbE involved in its anticonvulsant and neuropotective activity.

Keywords Ginkgo biloba, kainic acid, GABA, anticonvulsant, glutamic acid decarboxylase (GAD)

1. Introduction

Many herbal products that have been demonstrated to have promising anticonvulsant activity (Samuels et al., 2008) are candidate to be included in therapeutic strategies of epilepsy particularly due to their considerable safety and lower side effects. *Ginkgo biloba* leaves standard extract (GbE-761) among these herbal products. The pharmacological activity of GbE-761 is related to two main pharmacologically active groups of compounds, the flavonoids and the terpenoids (Smith and Luo, 2004). The flavonoid content in the GbE-761 is known to act mainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators (DeFeudis and Drieu, 2000). Two types of terpenoids are present in GbE-761: ginkgolides and bilobalidee (Smith and Luo, 2004). Ginkgolides are diterpenes with 5 types A, B, C, J, and M, where types A, B, and C account for around 3.1% of the total ginkgo leaf extract (DeFeudis and Drieu, 2000). Bilobalidee, a sesquiterpene trilactone, accounts for the remaining 2.9% of the total standardized ginkgo leaf extract (Smith and Luo, 2004). GbE-761 has shown beneficial effects in treating neurodegenerative diseases like Alzheimer's, cardiovascular diseases, cancer, stress, memory loss, tinnitus, geriatric complaints like vertigo, age-related macular degeneration, and psychiatric disorders like schizophrenia (Ramassamy et al., 2007; Mahadevan and Park, 2008). However, the anticonvulsant effect of

GbE-761was not sufficiently studied and the available data about the effect of GbE-761 on the epileptic activity and effectiveness of co-administered anticonvulsant drugs are controversial.

Some studies indicated that GbE-761 may have anticonvulsant activity. Ilhan et al., (2006) found that GbE-761 can protect against development of seizures and increases the anticonvulsant activity of valproic acid against pentylenetetrazole (PTZ)-induced kindling in mice. Sasaki et al., (1997) reported that bilobalide, a constituent of GbE-761, has anticonvulsant activity and correlated this effect with bilobalide ability to stimulate the hepatic metabolizing enzymes.

On the other hand, some other studies reported that GbE-761can precipitate epileptic seizures in well-controlled patients with epilepsy (Granger, 2001; Gregory, 2001). Manocha et al., (1996) reported that, GbE-761decreases the protective effect of both sodium valproate and carbamazepine.

The aim of this work is to study the anticonvulsant effect of chronic administration of GbE-761 for 15 days, in different dose levels, against kainic acid-induced seizures in mice. In addition to studying the possible involvement of the GABA-ergic transmission in the anticonvulsant, effect of GbE-761.

2. Materials and Methods

2.1. Animals

Male adult Swiss-Webster mice weighing 22-25 g from the Animal house of King Saud University were used in all experiments. Mice were housed in plastic cages with stainless steel mesh covers under a 12 h light/dark cycle at 25 o C and allowed free access to water and food (laboratory chow) ad libitum. The animal-testing protocol used in the present investigation was approved by the Institutional Animal Ethics Committee. All efforts were made to minimize animal suffering.

2.2. Chemicals

Standard Ginkgo biloba L. extract (GbE-761), kainic acid, Albumin bovine serum, Cohn fraction V, Folin and Ciocalteu's Phenol reagent, Sodium tartrate, Copper sulfate and glutamate assay kit were purchased from (Sigma, USA). GABA mouse ELISA assay kit and GAD mouse ELISA assay kit were purchased from Cusabio Biotech co., China. All other chemicals were of analytical grade.

2.3. Experimental protocol

The total number of animals that were used in this study was 50 mice. Animals were divided into five groups, ten mice for each. Group (1): Negative control treated with the vehicle; Group (2): KA control; treated with the vehicle for 15 days and KA at the time of anticonvulsant testing. Groups (3), (4) and (5) were treated with GbE-761 in the doses (20, 30, and 50 mg/kg/day) for 15 days respectively and KA at the time of anticonvulsant testing. The dose of GbE-761 dry extract was calculated for each animal; suspended in distilled water and given orally by gavage. In the day 15 of treatment and after administration of the last dose of GbE-761 by 1h, animals were subjected to testing of anticonvulsant activity. Thirty minutes later, animals in each group were sacrificed by decapitation. The brain of each animal was removed, rinsed in ice-cold saline, carefully blotted, weighed, homogenized in phosphate buffer (pH 7.4) and used for biochemical assays.

2.4. Kainic acid-induced seizure test

The test was performed according to the procedures described by Gupta et al. (2002). One hour later after the last treatment of animals with GbE, mice in both control and tested groups were administered KA at a dose 10 mg/kg, i.p. pH was adjusted to 7.2 ± 0.1. Animals were then observed for behavioral changes (forelimb clonic seizures, grooming, rearing, hind limb scratching, wet dog shakes, jaw movements, salivation, and head nodding). Time before onset of clonic convulsions and the percentage of seizures and mortality over a total period of 1 h were recorded.

2.5. Biochemical Assays

2.5.1. Determination of GABA and Glutamate levels

For determination of GABA and glutamate levels, perchloric acid (1mol/l) was added to an equal volume of the homogenate and mixed by vortexing. The mixture was allowed to stand for 5 min at room temperature. After centrifugation for 5 min, the supernatant was collected. The GABA content of the neutralized supernatant was assayed according to manufacture protocol of the mouse GABA autoantibody IgG ELISA Kit (Cusabio Biotech co.). Briefly, the microtiter plate provided in this kit has been pre-coated with an antibody specific to GABA. Standards or samples were added to the appropriate microtiter plate wells with a biotin-conjugated antibody preparation specific for GABA and Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. Then a TMB (3,3',5,5' tetramethyl-benzidine) substrate solution was added to each well. Only those wells that contain GABA, biotin-conjugated antibody and enzyme-conjugated Avidin exhibited a change in color. The enzyme-substrate reaction was terminated by the addition of sulphuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of GABA in the samples was then determined as mmol/mg protein by comparing the optical density of the samples to the standard curve.

The glutamate content in the supernatant was measured spectrophotometrically according to the method described by Lund (1986). The assay depends on enzymatic dehydrogenation with conversion of NAD+ to NADH. The concentration of glutamate in the samples was calculated as mmol /mg protein. A standard reference curve was plotted for each assay.

2.5.2. Determination of GAD activity

Glutamic acid decarboxylase activity in brain homogenate was determined by using Mouse glutamic acid decarboxylase autoantibody IgG (GAD-IgG) ELISA Kit (Cusabio Biotech co., China). The assay was performed according to the provider manual.

Briefly, the microtiter plate provided in this kit has been pre-coated with purified GAD antigen. Samples are then added to the appropriate microtiter plate wells and incubated. Then Horseradish Peroxidase (HRP)-conjugated anti-mouse IgG was added to each well and incubated. Finally, a TMB (3,3',5,5' tetramethyl-benzidine) substrate solution was added to each well. The enzyme-substrate reaction was terminated by the addition of a sulphuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. GAD activity was calculated as mmol /min/mg protein.

2.5.3. Determination of protein content

Protein content in brain homogenate was measured by biuret method using bovine serum albumin as standard (Lowrey et al., 1951).

2.6. Statistical analysis

The variability of results was expressed as the mean ± SEM. The significance of differences between mean values was determined using one-way analysis of variance (ANOVA) followed by Tukey's post hoc comparison between groups. P< 0.05 represents level of significance.

3. Results

3.1. Protective effect of GbE-761 against KA-induced seizures

Administration of kainic acid in a dose 10 mg/kg, i.p produced clonic seizures in 100 % and mortality in 40 % of tested animals with seizure onset 45.7 ± 2.7 sec. as shown in Table 1. Administration of GbE-761 in doses 20, 30 and 50 mg/kg/day, orally (p.o) for 15 days significantly increased the time of onset of seizures with doses of 20 and 30 mg/kg ($p < 0.05$) and with 50 mg/kg ($p < 0.01$). Percent seizures were reduced to 60, 30, 10 % respectively and percent mortality was reduced to 10, 0 and 0 % respectively in animals treated daily by GbE-761 in doses 20, 30 and 50 mg/kg for 15 days.

3.2. Effect of GbE-761 on brain Glutamate level

As shown in Fig. 1, the level of glutamate was significantly elevated in brain of KA-treated animals relative to its level in control animals. GbE-761 significantly reduced brain glutamate concentration in a dose 20 and 30 mg/kg ($p< 0.05$) and in dose of 50 mg/kg ($p < 0.01$) relative to KA-treated group.

3.3. Effect of GbE-761 on brain GABA level

Treatment of animals with KA caused insignificant change in brain GABA content relative to control. Administration of GbE-761 significantly increased brain GABA level in dose 20 mg/kg ($p <0.05$) and in doses of 30 and 50 mg/kg ($p< 0.01$) relative to GABA level in KA-treated group as shown in Fig 2.

3.4. Effect of GbE-761 on brain GAD activity

KA administration caused a significant decrease in brain GAD activity relative to control. GAD activity was significantly elevated after treatment with GbE-761 in doses 20, 30 mg/kg ($p < 0.05$) and with 50 mg/kg ($p< 0.01$), as shown in Fig. 3.

Table 1. Statistical analysis of the time of onset of seizures resulted from the effect of *Ginkgo biloba* extract (GbE-761) (20, 30, and 50 mg/kg per day, p.o) for 15 days against KA (10 mg/kg, i.p) -induced seizures in mice.

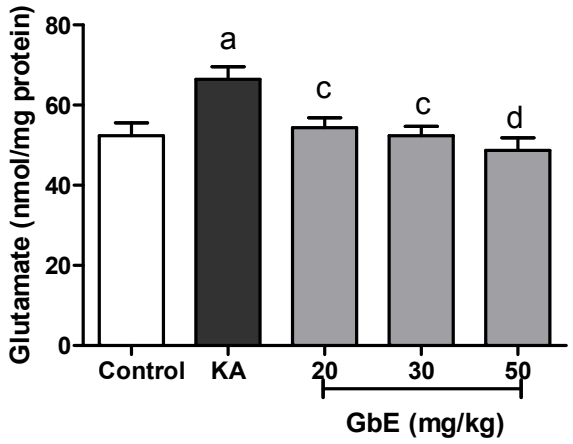
Treatment (mg/kg)	Time onset of seizure (seconds)
Control	00
KA (100)	45.23 ± 5.72[a]
GbE (20)	63.35 ± 4.27[b,c]
GbE (30)	65.35 ± 5.24[b,c]
GbE (50)	72.14 ± 4.18[b,d]

Values presented as the mean ± SEM (n=10).
[a] *p< 0.05 vs. control.*
[b] *p< 0.01 vs. control.*
[c] *p< 0.05 vs. KA-treated group.*
[d] *p< 0.05 vs. KA-treated group.*

Table 2. Statistical analysis of seizures and mortality of resulted from the effect of *Ginkgo biloba* extract (GbE-761) (20, 30, and 50 mg/kg per day, p.o) for 15 days against KA (10 mg/kg, i.p) -induced seizures in mice.

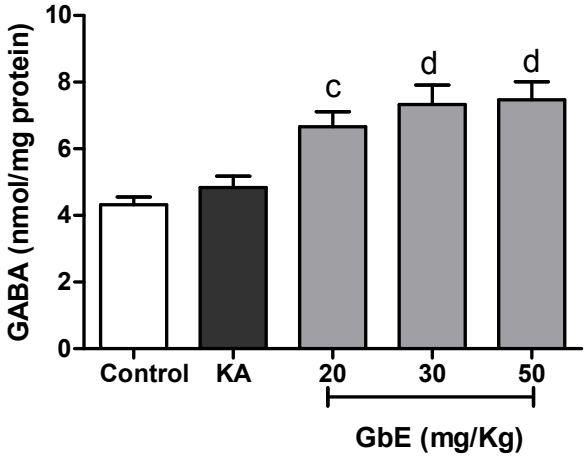
Treatment (mg/kg)	Seizure %	Mortality %
Control	00	00
KA (100)	100[b]	40[b]
GbE (20)	60[c]	10[d]
GbE (30)	30[d]	0[d]
GbE (50)	10[d]	0[d]

Values presented as the mean ± SEM (n=10).
[a] *p< 0.05 vs. control.*
[b] *p< 0.01 vs. control.*
[c] *p< 0.05 vs. KA-treated group.*
[d] *p< 0.05 vs. KA-treated group.*



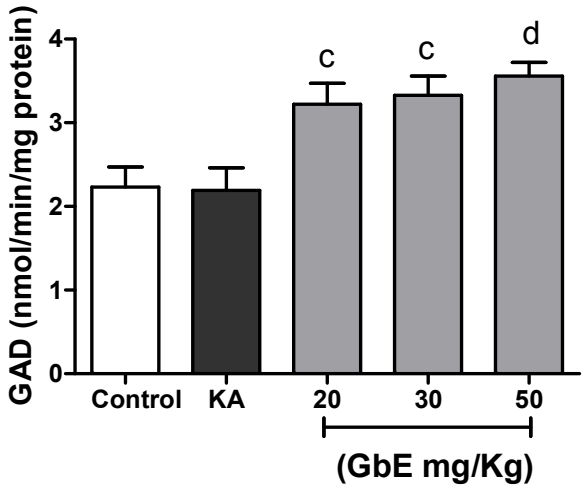
Control	KA	GbE 20	GbE 30	GbE 50
52.35 ± 3.22	66.43 ± 3.15[a]	54.36 ± 2.45[c]	52.34 ± 2.37[c]	48.67 ± 3.14[d]

Fig 1. Effect of *ginkgo biloba* extract (GbE-761) (20, 30 and 50 mg/kg/day, p.o) for 15 days on brain glutamate concentration after KA-induced seizures in mice. Results represent mean ± SEM (n=10). [a] p< 0.05 vs. control. [c] p< 0.05 vs. KA-treated group. [d] p< 0.01 vs. KA-treated group.



Control	KA	GbE 20	GbE 30	GbE 50
4.32 ± 0.23	4.84 ± 0.34	6.66 ± 0.45[c]	7.33 ± 0.58[d]	7.47 ± 0.54[d]

Fig 2. Effect of *ginkgo biloba* extract (GbE-761) (20, 30 and 50 mg/kg/day, p.o) for 15 days on brain GABA concentration after KA-induced seizures in mice. Results represent mean ± SEM (n=10). [c]p< 0.05 vs. KA-treated group. [d] p< 0.01 vs. KA-treated group.



Control	KA	GbE 20	GbE 30	GbE 50
2.23 ± 0.24	2.19 ± 0.27	3.22 ± 0.25[c]	3.33 ± 0.23[c]	3.56 ± 0.16[d]

Fig 3. Effect of *ginkgo biloba* extract (GbE-761, 20, 30 and 50 mg/kg/day, p.o) for 15 days on brain glutamic acid decarboxylase (GAD) activity after KA-induced seizures in mice. Results represent mean ± SEM (n=10). [c] p< 0.05 vs. KA-treated group. [d] p< 0.01 vs. KA-treated group.

4. Discussion

In the present study, we investigated the possible anticonvulsant activity of GbE-761 using one of the widely used animal models in testing the anticonvulsant activity using KA-induced seizures test in mice. Moreover, the possible involvement of glutamate/GABA-ergic transmission in this effect was studied.

Kainic acid (a glutamate analogue) has been used by many researchers to induce seizures that are thought to mimic the pathological state of epilepsy and other convulsive disorders (Lothman and Collins 1981; Armstrong et al., 1986). It acts as agonist on the excitatory glutamate kainate receptors and induces seizures, neurotoxicity and neuronal damage (Järvelä et al., 2011). Our results showed that, injection of KA in animals in a dose 10 mg/Kg i.p. induces clonic seizures and mortality as shown in Tabel 1. The effect of KA was accompanied with increase in brain glutamate.

Previous studies indicated that KA seizures are associated with an increase in levels of extracellular glutamate and this appears to be associated with generation of lipid free radicals and with a decrease in residual antioxidant effects (Ueda et al., 2002). The effect of KA in our results was accompanied with a decrease in brain GAD activity without significant change in brain GABA level.

Shaffer and Meserve (1989) reported that, the levels of GABA in the brain were found to increase in KA-injected animals over control. He suggested that GABA levels may actually increase in response to convulsions and serve to negatively feed back to its synthetic enzyme. Therefore, a decrease in GAD activity would not necessarily reflect a decrease in GABA levels.

Treatment with GbE-761 in doses 20, 30 and 50 mg/kg/day, p.o for 15 days showed protection of animals against KA-induced seizures. This effect appeared in form of reduction in percentage of seizures and mortality and increase in seizure time of onset. These results indicated that GbE-761 has anticonvulsant activity against KA-induced convulsions. These results may be in accordance with the results recorded by Ilhan et al., (2006) indicating that GbE-761 can protect mice against PTZ-induced kindling seizures.

GbE-761 has a potent antioxidant effect (Goh and Barlow, 2002 ; Rhein et al., 2010). Hence, the observed anticonvulsant effect of GbE-761 may be related to the antioxidant effect of GbE-761. But other studies indicated that antioxidant effects do not contribute in the anticonvulsant activity against KA-induced seizures (Yalcin, 2004; Akcay et al., 2005).

Measurements of brain biochemical changes showed a dose related decrease in brain glutamate and increase in GABA levels and increase in GAD activity in the groups treated with GbE-761 relative to the untreated group. These results indicated that the anticonvulsant effect of GbE-761 is to some extent correlated to the changes in the GABA-ergic transmission.

GABA is a major inhibitory neurotransmitter in the central nervous system. It is synthesized by the decarboxylation of glutamic acid via the action of the enzyme glutamic acid decarboxylase (GAD). After release from the presynaptic terminal, GABA is either taken up into the mitochondria of neurons and glial cells, or is degraded to succinic semialdehyde by the actions of GABA transaminase (GABA-T) enzyme.

The role of GABA in the control of generalized seizures in laboratory animals has been well documented. A number of studies have shown that GABA or its analogues such as muscimol, when administered centrally, have controlled seizures induced by GABA antagonistic convulsants such as

bicuculline (Iodorola and Gale, 1982) and kainic acid (KA) (Albala et al., 1984).

Hence, from these data and from our results we can correlate between the observed anticonvulsant effects of GbE-761 and its ability to increase brain GABA level. This effect may be mediated through activation of GAD which converts glutamate to GABA. This can explain the observed GbE-761-induced decrease in brain glutamate concentrations.

These changes also indicate that, GbE-761 enhances GAD activity which converts glutamate to GABA. This led to the observed reduction in brain glutamate and elevation in brain GABA. According to Mahady (2001), the neuroprotective effect of GbE-761 is attributed to its major flavonoid constituent bilobalide.

Bilobalide is a flavonoid present in GbE-761 in measurable concentrations and has the ability to decrease brain glutamate and increase brain GABA via stimulation of GAD activity (Sasaki et al., 1999).

Although the increase in GABA in our results was accompanied with increase in GAD activity, the effect of GbE-761 on GABA release cannot be omitted, where Jones et al., (2002) showed that, bilobalide has the ability to stimulate GABA release in cerebral neurons.

In a conflict with our results, some studies correlate the neauroprotective effect of bilobalide to its antagonistic activity on GABAA receptors (Kiewert et al., 2007). Moreover, a pharmacokinetic aspect in the anticonvulsant effect of GbE-761 may be involved where, Sasaki et al., (1997) reported that bilobalide has a hepatic metabolizing enzyme activity and correlate this effect to its anticonvulsant activity.

Conclusion

Our study showed that, GbE-761 has anticonvulsant activity against KA-induced seizures. This anticonvulsant effect may be mediated by different mechanisms, but our study revealed the involvement of GABA-ergic transmission in this effect via stimulating GAD activity, reducing the brain glutamate and increasing brain GABA levels, the effect which are related to the bilobalide content of GbE-761.

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الملخص العربي

إشتراك نظام توصيل الجابا في التأثير المضاد للتشنج لعقار الجنكجو بايلوبا ضد النوبات الصرعية المحدثة بواسطة حامض الكاينيك في الفئران الصغيرة

باسل عبد النعيم عبد الوهاب[1] و متولي السيد متولي[2] و سعيد سعيد الشماع[2]

يعتبر عقار الجنكجو بايلوبا من المنتجات النباتية التي أثبتت الدراسات فاعليته في علاج العديد من الاضطرابات العصبية. في حين أن التأثير المضاد للتشنج لهذا العقار لم يتم دراسته بصورة كافية. و من ثم كان الهدف من هذا البحث هو دراسة التأثير المضاد للتشنج لمستخلص عقار الجنكجو بايلوبا و دراسة دور نظام نقل الجابا في المخ في هذا التأثير. الطريقة: تم دراسة التأثير المضاد للتشنج لمستخلص عقار الجنكجو بايلوبا في جرعات 20 و30 و50 مجم/كجم و التي تم إعطائها عن طريق الفم لمدة خمسة عشر يوما في الفئران قبل إحداث التشنجات فيها بواسطة حقنها بمادة حامض الكاينيك. أيضا تم تعيين مستوى مادتي الجلوتامات و الجابا و نشاط إنزيم الجلوتامات ديكاربوكسيليز في مخ الفئران المعالجة. النتائج: أظهرت النتائج قدرة عقار الجنكجو بايلوبا على حماية الفئران من التشنجات المحدثة بواسطة حامض الكاينيك في تأثير مرتبط بالجرعة المستخدمة، ظهر ذلك في صورة زيادة اعتبارية في زمن حدوث التشنجات ونقص في نسبة التشنجات و الموت في الفئران المعالجة بعقار الجنكجو بايلوبا. أيضا أظهرت النتائج وجود انخفاض في مستوى الجلوتامات بالإضافة إلى زيادة في مستوى الجابا و نشاط إنزيم الجلوتامات ديكاربوكسيليز في مخ الفئران المعالجة بعقار الجنكجو بايلوبا قبل حقنها بحامض الكاينيك. الخلاصة: من نتائج هذه الدراسة يمكن الوصول إلى أن لمستخلص نبات الجنكجو بايلوبا تأثير مضاد للتشنجات ضد التشنجات المحدثة كيميائيا بواسطة حامض الكاينيك. هذا التأثير قد يعزى إلى العديد من الآليات إلا أن نتائج هذه الدراسة أظهرت الدور الهام لنظام توصيل الجابا في المخ في هذا التأثير. ومن ثم فإن التوجه في الأبحاث المستقبلية في هذا المجال يجب أن يوجه في اتجاه كشف الآليات الأخرى التي تشارك في التأثير المضاد للتشنج و التأثير الواقي للأعصاب لعقار الجنكجو بايلوبا.

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