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PHARMACODYNAMIC INTERACTION BETWEEN NIFEDIPINE AND SODIUM VALPROATE AGAINST KAINIC ACID-INDUCED CONVULSOINS IN MICE

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ABSTRACT :

In the present study, the possible pharmacodynamic interaction between nifedipine (30 mg/kg,i.p) and sodium valproate (300 mg/kg,i.p) against kainic acid (70 mg/gk, i.p) was evaluated in mice. The seizures onset of kainic acid (KA), the percent of mice surviving KA-induced seizures and the mean survival time (MST) of mice were determined 30 minutes after single and combined administration of nifedipine and sodium valporate (VAL). The above mentioned three parameters of KA-induced seizures were determined in a control group of mice receiving saline solution.

In a second set of experiments, the serum and brain Na^+, Ca^{2+} and K^+ ion contents were determined after single i.p. administration of KA, nifedipine and VAL. Two lesser than the MST of mice receiving KA, mice were given nifedipine plus KA, VAL plus KA and nifedipine plus VAL and KA. Serum and brain tissue samples were taken from all groups of mice and were analysed for their content of Na^+, Ca^{2+} and K^+ ion

Results of this study revealed that the i.p injection of KA into mice led to the appearance of convulsions (seizure onset) after 6.06 minutes and a MST of mice of 7.82. minutes. This convulsive effect was associated with significant increase in brain Na^+ and Ca^{+2} levels as well as significant lowering of brain K^+ concentration. Our results also indicated that the i.p. injection of nifedipine into mice produced significant increase in the seizure onset of KA action and the MST of mice as well as, the percent protection of mice to a value of 25%. The anticonvulsant action of VAL was accompanied by a significant increase in the serum Na^+ and Ca^{2+} contents and an elevated brain K^+ level.

In addition, our results indicated that the single i.p injection of VAL elicited significant increases in the onset of KA-induced seizures, the MST of mice as well the KA-induced

mortality by a factor of 50%. This effect was correlated with an increase in the serum Na^+, lowered brain Na^+ and an increased brain K^+.

The combined administration of nifedipine and VAL was found to protect all animals from KA-induced death. This 100% protection was associated with 4-fold increase in the onset of KA-induced seizures. Measurement of the serum and brain electrolytes in mice receiving the combination of nifedipine and VAL demonstrated that this combination caused significant diminution of brain Na^+ and Ca^{2+} ions and a rise in brain K^+ ions.

It may be the ability of nifedipine to reduce brain Na^+ and Ca^{2+} concentration which is the factor responsible for the additive anticonvulsant effect recorded after the combined administration of nifedipine and sodium valproate.

INTRODUCTION :

Calcium antagonists is a diverse class of drugs that are widely used either alone or concurrently with other drugs in the treatment of different disease states such as angina pectoris, hypertension and other cardiovas-cular disorders. Many of them are also used in varieties of non-cardiovascular disorders such as prophylaxis of migraine, bronchial asthma and recently they are tried in the treatment of epilepsy [1] .

Nifedipine is one of the calcium influx blockers, belonging to the dihydropyridine chemical family, was reported to have anti-convulsant properties. Several reports are now available indicating the effectiveness of nife-dipine against experimental models of epi-lepsy.

Nifedipine was reported to be effective in protection of laboratory animals against pentrylenetetrazole-induced seizures [2-4]. Other reports indicated that nifedipine is effective against electric shocks involving the supramaximal ones [5,6].

Tussel [3] reported that nifedipine is more effective than verapamil in antagonizing the chemically-induced seizures, induced by diffe-rent chemical agents. Besides, Kamal et al., [7] showed moderate effectiveness of nifedipine in antagonizing PTZ-induced seizures when it was given to rats in a dose of l0 mg/kg. Similarly Wong et al.[8], reported that nifedipine in a dose of 20 mg/kg produced potential antiepileptic activity against convul-sions induced by chemical and electrical stimuli in mice. The authors refered to the correlation between this anticonvulsant prope-rties of nifedipine and its ability to inhibit Ca^{2+} influx to the neurons. Besides, this report pointed out to the highest anticonvu-lsant properties of nifedipine than other Ca^{2+} antagonists.

Regarding the interaction of calcium entry blockers with antiepileptic drugs [9] stated that the concurrent administration of nifedipine with phenobarbitone, diazepam and sodium valproate led to significant potentiation of the

anticonvulsant activity of these classical anti-convulsant drugs. Other reports indicated that nifedipine moderately potentiates the anti-convulsant activity of phenobarbitone and valproate against both electrically-induced convulsions and PTZ-induced seizures in mice [10,11]. The authors also reported that nifedipine reduces the ED_{50} value of valproate against PTZ-induced convulsions by a factor of 12-fold. Moreover, the concurrent administra-tion of nifedipine with the classical anti-epileptic agents such as phenytoin, and carba-mazepine decreased the ED_{50}. values of these drugs against chemically-induced seizures in mice.

Valproic acid, is known to be one of the widely used antiepileptic drugs and its wide-spread use is related to its effectiveness against different types of seizures, in addition to its low adverse effects compared with other anti-epileptic drugs [12].

The exact mechanism of valproic acid anticonvulsant action is not clearly known but, one of the most important possible mechanisms of action, is that by which this drug is acting through blocking the T-type calcium channels in the nerve cells, thereby reducing the Ca^{2+} current and neuronal excitability.

Hence, the interaction of drugs affecting calcium channels, such as nifedipine with valproic acid may provide a potential benefit in potentiating the anticonvulsant action of valproic acid. Therefore the combined use of calcium antagonists with valproic acid may allow more effective control of seizures. Meanwhile, it permits the reduction of the dose of valproic acid and consequently decrea-ses its possible side effects.

In the present study, an attempt was undertaken to evaluate the possible interaction between nifedipine in a dose of 30 mg/kg, i.p. and sodium valproate in a dose of 300 mg/kg, i.p regarding their anticonvulsant activity against kainic acid-induced seizures in mice.

An attempt was undertaken to find out a correlation between the changes in the anticonvulsant activity of sodium valproate, nifedipine and their combination with their ability to produce alterations in serum and brain electrolytes. Thus, the present study aims also at measuring the serum and brain concentrations of Na^{+}, Ca^{2+} and K^{+} ions in control mice as well as in mice treated with nifedipine (30 mg/kg, i.p), sodium valproate (300 mg/kg, i.p) and their combination.

EXPERIMENTAL :

Material and Methods :

Animals:

All experiments were performed using albino mice of either sex received from the Animal House, Faculty of Medicine, Assiut University. All mice were weighing 18-20g. They were adapted in the laboratory for one week before the day of experimentation. Each mouse was used only once. The animals were kept in groups in standard nacrolane cages at room temperature of 30-35°C and humidity of 50-60% with free access to water and standard ration ad libitum. To minimize the possible bias

of circadian rhythm, all drugs were admi-nistered in the morning.

Chemicals:

1-Kainic acid (KA) : (Sigma)

The drug was supplied in a powder form and prepared in solution by dissolving it in double-distilled water alkalinized by Na OH to pH of 8.4.

2- Sodium valproate: (Sigma)

The drug was supplied in a hygroscopic form which is highly water soluble. It was dissolved in double-distilled water to prepare the solution just before the experiments were carried out.

3- Nifedipine: (Sigma)

The drug was supplied as yellow crystals which are insoluble in water. These crystals were dissolved in a mixture of alcohol and propylene glycol to form a solution, which was diluted by double-distilled water.

Determination of the Effect of Drugs on Seizure Onset of Kainic Acid, Mean Survival Time (MST) of Mice and Percent Protection of Mice from Kainic acid-induced Mortality :

This test was performed according to Chambon et al.[13]. This group of experiments consisted of four sets. Animals in each set were divided into 8 groups, each consisting of 8 mice. In the first set of experiments the following protocol was conducted:

1-First group of animals (control) were injected i.p with the ED_{100} of KA (70 mg/kg) dissolved in double-distilled water.

2-Second group of animals were injected i.p. with sodium valproate (300 mg/kg), 30 min. before the injection of the ED_{100} of KA.

3-Third group animals were injected i.p. with nifedipine (30 mg/kg) 30 minutes before the injection of KA in a dose of 70 mg/kg.

4-Fourth group animals were injected i.p. with sodium valproate (300 mg/kg) + nifedipine (30 mg/kg), 30 minutes before the i.p. injection of KA (70 mg/kg).

In each group, animals were observed for 30 minutes for appearance of clonic hind limb extensions and death. Onset of the appearance of seizures, MST of mice and percent of surviving mice following KA administration were determined in each group.

Measurement of serum and brain electro-lytes :

Thirty minutes before induction of seizures by KA , groups of mice were i.p. injected with nifedipine (30 mg/kg), and sodium valproate (300, mg/kg). Two minutes lesser than the MST of mice treated with KA (the time of peak convulsive effect); animals were decapitated and their brains were immediately dissected out and blot between two damp filter papers then weighed. Samples of blood were obtained in heparinized tubes and kept at 4°C until they were analyzed.

Thirty minutes before induction of seizures by KA, other groups of mice were injected i.p. with nifedipine, (30 mg/kg) in combination with sodium valproate (300, mg/kg, i.p). Two minutes lesser than the MST of each mouse animals were dealt with as described above to obtain blood and brain samples.

Blood samples of about 2 ml and brain tissue of approximately 100 mg were taken from the previously mentioned groups of animals described above. Blood samples were left to clot and the serum was separated by centrifugation. Brain tissue samples were mixed with 5 ml of 0.4 N perchloric acid, homogenized and centrifuged at 40,000 rpm for 20 minutes and then the supernatant fraction was obtained.

Serum and brain-supernatant samples were diluted with double distilled water and their electrolyte contents were determined by photoelectric flame photometry for Na^+, K^+, and Ca^{2+} ions. Electrolyte levels in both serum and brain tissue were also determined in a control group of animals. Standard calibration curves for Na^+, K^+, and Ca^{2+} ions were constructed by preparing standard solutions of NaCl, KCl, and $CaCl_2$ using analar sources of these salts. The standard calibration curves were used for the determination of the plasma and brain contents of Na^+, K^+, and Ca^{2+} separately.

Statistical analysis :

The variability of samples is expressed as the mean ±standard error of the mean. The significance of difference between samples was determined using student's t-test [14]. The differences were regarded as significant when $P<0.05$ and highly significant when $P<0.01$.

RESULTS :

Effect of Kainic acid:

The i.p administration of kainic acid (KA) in a dose of 70 mg/kg into mice caused the characteristic clonic limb seizures (piano-playing convulsions) and mortality of tested animals with a seizure onset of KA of 6.06 minutes and the recorded mean survival time of mice was 7.82 minutes (Table 1).

The anticonvulsant activity of drugs

1- Effect of Sodium Valproate :

The prior treatment of animals with sodium valproate in a dose of 300 mg/kg, i.p, 30 minutes before the i.p. injection of kainic acid manifested a highly significant prolon-gation in the seizure onset of KA from 6.06 to 12.63 minutes. There was also an elevation in the percent of animals protected from KA-induced death to a value of 50% and a highly significant increase in the MST of mice from 7.82 to 14.67 minutes relative to the control KA-treated group of animals (Table 1).

2- Effect of Nifedipine :

The pretreatment of mice with nifedipine in a dose of 30 mg/kg, i.p, 30 minutes before the injection of kainic acid elicited a highly significant increase in the seizure onset of KA from 6.06 to 10.78 minutes and an increase in the percent of animals protected from KA-induced death to 25%. There was also a

highly significant increase in the MST of mice from 7.82 to 17.95 minutes compared with the control KA-treated group (Table 1).

Table (1): Effect of KA, sodium valproate, nifedipine and their combination on seizure onset, % protection of mice from death and mean survival time of mice following induction of seizures by i.p. injection of kainic acid (KA) in a dose of 70 mg/kg.

Drug dose (mg/kg)	Seizure onset (min)	No of dead animals	% protection from death	Mean survival time (min)
Control	6.06±0.27	8/8	0.00	7.82±0.81
Sodium valproate (300)	12.63±1.34**	4/8	50.00	14.67±1.92**
Nifedipine (30)	10.78±0.75**	6/8	25.00	17.95±1.02**
Valproate (300)+Nifidipine (30)	23.84±1.04**	0/8	100.00	30.00±0.00**

Results represent the mean of 8 experiments ± standard deviation.
** Highly significant difference from the control KA- treated group (P<0.01).

3-Effect of a Combination of Sodium Valp-roate and Nifedipine :

The combined administration of nifedipine (30 mg/kg, i.p) with sodium valproate (300 mg/kg i.p), 30 minutes before the i.p. injection of kainic acid produced a highly significant increase in both the seizure onset of KA from 6.06 to 23.84 minutes and the MST of mice from 7.82 to 30 minutes. In addition, there was an increase in the percent of animals protected from KA-induced death from 0% to 100% in comparison with the control KA-treated group (Table: 1).

Relative to the valproate-treated group of mice, there was a highly significant increase in both the seizure onset of KA from 12.63 to 23.84 minutes (Fig. 1A). and the MST of mice from 12.63 to 23-84 minutes (Fig. 1A). Moreover, there was an increase in the percent of animals protected from KA-induced mortality from 50% to 100% (Fig. 1B).

III-Effect of drugs on serum and brain electrolyte Levels:

1- Effect of sodium valproate:

Table (2) shows that the pretreatment of animals with sodium valproate in a dose of 300 mg/kg, i.p, 30 minutes before the injection of kainic acid caused a significant increase in the serum sodium level from 136.92 mEq/L to 138.82 mEq/L. In addition, there was a highly significant increase in the brain potassium level from 90.05 to 94.14 mEq/kg and a highly significant decrease in the brain sodium level from 76.15 to 70.38 mEq/kg and the brain calcium level from 9.54 to 7.50 mEq/kg compared with the control KA-treated group of mice (Table 2).

Fig. (1) : Effect of nifedipine (NIF) on (A) seizure onset and mean survival time, (b) percent protection from death of sodium valproate (VPA) against kainic acid-induced seizures in mice.
Results represent the mean of 8 experiments ± standard deviation.
**** Highly significant difference from valproate group ($p<0.01$) .**

2- Effect of Nifedipine:

As it is evident from table 2, the pretreat-ment of animals with nifedipine in a dose of 30 mg/kg, i.p, 30 minutes before the i.p. injection of kainic acid led to a significant decrease in the serum sodium level from 136.92 to 133.28 mEq/L and a significant increase in the serum calcium level from 9.03 to 11.95 mEq/L. Besides, there was a highly significant increase in the brain potassium level from 90.05 to 96.13 mEq/kg. In contrast, a highly significant decrease in the brain sodium level from 76.15 to 66.22 mEq/kg and the brain calcium level from 9.04 to 6.33 mEq/kg were observed compared with the control KA-treated group of animals (Table 2).

3- Effect of a Combination of Sodium Valproate and Nifedipine:

The combined i.p. administration of valproate into mice in a dose of 300 mg/kg, and nifedipine in a dose of 30 mg/kg, before the i.p. injection of kainic acid brought about a highly significant increase in the brain potassium level from 90.05 to 97.31 mEq/kg and a highly significant decrease in both brain sodium level from 76.15 to 63.98 mEq/kg and brain calcium level from 9.54 to 5.53 mEq/kg compared with the control KA-treated group of mice (Table 2). There was a highly significant decrease in the brain sodium level from 70.38 to 64.12 mEq/kg (Fig 2-A) and the brain calcium level from 7.50 to 4.28 mEq/kg (Fig. 2-B). Moreover, there was

a highly significant increase in the brain potassium level from 94.14 to 98.37 mEq/kg (Fig 2-B) compared with the valproate-treated group (Fig. 2-B).

Table (2): Effect of sodium valproate, nifedipine, and their combination on serum and brain electrolyte levels in mice following induction of seizures by i.p. injection of kainic acid (KA) in a dose of 70 mg/kg.

Drug dose (mg/kg)	Serum electrolytes (mEq/L)			Brain electrolytes (mEq/kg)		
	Na^+	K^+	Ca^{2+}	Na^+	K^+	Ca^{2+}
Control	136.92±1.63	8.53±0.58	9.03±0.33	76.15±0.72	90.05±0.85	9.54±0.33
Valproate (300)	138.82±060*	8.20±0.42	9.23±085	70.38±0.63**	94.14±0.90**	7.50±1.14*
Nifedipine (30)	133.28±1.44*	8.36±0.63	11.95±1.05*	66.22±1.42**	96.13±1.50**	6.33±0.54**
Valproate (300) + Nifedipine (30)	137.51±0.26	8.41±048	8.89±0.59**	64.12±0.87**	98.37±0.42**	4.28±0.19**

Results represent the mean of 8 experiments ± standard deviation.
*** Significant difference from the control KA-treated group ($p<0.05$).**
**** Highly significant difference from the control KA-treated group ($p<0.001$).**

Fig. (2) : Influence of nifedipine (NIF) on sodium valproate-induced changes in (A) serum, (B) brain electrolyte

levels in kainic acid- treated mice.
Results represent the mean of 8 experiments ± standard deviation.
** Highly significant difference from valproate group ($p<0.01$) .

DISCUSSION :

It is well known that kainic acid is a common convulsive agent that exerts its action through stimulation of the specific receptors of the excitatory amino acid, glutamate present in the brain [15].

The i.p. administration of sodium valproate into mice in a dose of 300 mg/kg was found to be effective in antagonizing the kainic acid-induced seizures. This antiepileptic drug was significantly able to delay the onset of kainic acid-induced seizure. Also it increased the percent of animals protected from death produced by KA and the MST of animals treated with KA. This antagonism of the kainic acid-induced seizures by sodium valproate may be explained partly on the basis of the inhibitory action of kainate to the specific receptors for the excitatory amino acid, glutamate present in the human and animal brain [16].

Our results showed that the i.p. administration of nifedipine produced signi-ficant anticonvulsant properties against kainic acid-induced convulsions. This calcium chann-el blocker was able to significantly delay the seizure onset of kainic acid, percent of animals protected from KA-induced death and the MST of mice i.p. injected with KA.

It has also been recorded that there was a significant potentiation in the anticonvulsant properties of sodium valproate after its concurrent administration with nifedipine. This was manifested by prolongation of the onset of seizure caused by kainic acid, as well as an increase in the percent of animals protected from kainic acid-induced mortality to 100%.

In this work, it was also designed to find out if there any correlation between the changes occurring in the anticonvulsant activity of valproic acid when used concurrently with nifedipine with their effects on the ion channels. To achieve this purpose we measured the corresponding changes in the brain and serum electrolytes after administration of each drug alone and a combination of the two drugs into mice.

It should be noted that the experimentally-induced epileptiform activity in laboratory animals by different methods such as electrical stimulation, injection of pentylenetetrazole or penicillin, topical neucortical application of alumina cream [17], bicuculline [18] or N-methyl-D-aspartate, kainate and quisqualate [19] is accompanied by an increase in the intracellular sodium and calcium ion concentrations as well as an increase in the extracellular potassium ion concentration.

It has been also reported that drugs which can pertain ionic gradients in the inhibitory sites in the brain (i.e: low intracellular sodium and calcium and high intracellular potassium ion concentrations) can also exhibit anti-epileptic activity in humans [20-21].

It is well documented that kainic acid is a common convulsive agent that exerts its action via stimulation of the specific receptors on

which the excitatory amino acid, glutamate, is acting. [15]. Regarding the anticonvulsant activity, the i.p. administration of sodium valproate into mice in a dose of 300 mg/kg, the drug was found to be effective in antagonizing the kainic acid-induced seizures. This drug significantly delayed the onset of kainic acid-induced seizures. It also increased the percent of animals protected from KA-induced lethal effect and the MST of animals. This antagonism of kainic acid-induced-seizures by sodium valproate may be interpreted partly on the basis of the antagonistic action of kainate to the specific excitatory amino acid glutamate on its specific receptor sites in the brain [16].

Results also indicated that the i.p. administration of nifedipine into mice caused significant anticonvulsant properties against kainic acid-induced convulsions. This calcium entry blocker significantly delayed the seizure onset of kainic acid, increased the percent of animals protected from KA- induced death and the mean survival time of mice injected with KA.

There was a significant potentiation in the anticonvulsant properties of sodium valproate after its concurrent administration with nifedipine. This was reflected by prolongation of the onset of seizure produced by kainic acid, as well as an increase in the percent of animals protected from kainic acid-induced mortality to 100%.

Measurements of serum and brain electrolytes in models of seizures induced by kainic acid were carried out. Results revealed that the i.p. administration of valproate leads to a decrease in both brain sodium and calcium levels and a significant increase in the brain potassium level. These results might indicate that the anticonvulsant action of valproate against kainic acid-induced convulsions is exerted by direct action of the drug on the ion channels in the CNS. It was also found that serum sodium level was significantly increased by valproate. However, this effect might be ascribed to the sodium content of sodium valproate salt rather than a direct effect on sodium channels.

It was also shown that Nifedipine significantly reduced the brain calcium level, an effect which can be attributed to its blocking properties of calcium channels. The drug also was able to decrease significantly the brain sodium and increase the brain potassium levels. These results are in support of the possible contribution of other ion channels to the anticonvulsant action of nifedipine against kainic acid-induced seizures. Besides, these results are in accordance with the previous suggestions by Shibuya and Watanabe [22]. The decrease in the serum calcium level produced by nifedipine may be related to blockade of tissue uptake of calcium ions subsequent to calcium channel blocking by this drug leading to increased renal excretion of calcium. Similarly, the significant decrease in the serum sodium level can be attributed to the increased renal sodium excretion by nifedipine [23].

The concomitant i.p. administration of sodium volproate with nifedipine into mice showed a significant decrease in the brain sodium and calcium as well as an increase in the

brain potassium level. These changes indicate that the potentiation exerted by nife-dipine to the anticonvulsant action of valproate are mostly due to an action on the ion channels in the CNS. The combined use of nifedipine with valproate in mice showed no alteration in the serum sodium level since this increase caused by sodium valproate was counter-balanced by the decrease produced by nife-dipine.

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دراسة التفاعلات الديناميكية الدوائية بين عقارى النيفيديبين وفالبروات الصوديوم ضد النوبات الصرعية المحدثة بمادة حامض الكاينيك فى الفئران

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فى هذا البحث تم دراسة التفاعلات الديناميكية الدوائية المحتملة بين عقارى النيفيديبين وفالبروات الصوديوم ضد النوبات الصرعية المحدثة بواسطة مادة حامض الكاينيك .

-وتم قياس الزمن اللازم لظهور النوبات التشنجية ونسبة الموت فى حيوانات التجارب بالإضافة إلى متوسط الأزمنة التى تبقى فيه الفئران حيه بعد حقن مادة حامض الكاينيك لوحدها وبعد مرور ٣٠ دقيقة من حقن كل من النيفيدبين وفالبروات الصوديوم كل على حده أو فى تعاطى مشترك.

- وكذلك تم قياس مستوى أيونات الصوديوم والكالسيوم والبوتاسيوم فى مصل ومخ الفئران بعد الحقن البريتونى لكل من حامض الكاينيك والنيفيديبن وفالبروات الصوديوم قبل انتهاء زمن بقاء الحيوانات حيه وعقب حقنها بحامض الكاينيك بدقيقتين .

- أظهرت النتائج أن حقن حامض الكاينيك فى الفئران يؤدى إلى ظهور نوبات صرعية بعد زمن ٦,٠٦ دقيقة من حقن المادة وأن متوسط زمن بقاء الحيوانات حيه قد وصل إلى ٧,٨٢ دقيقة. وأظهرت النتائج أيضاً أن هذه النوبات الصرعية تكون مصحوبة بزيادة ملحوظة فى مستوى الصوديوم والكالسيوم ونقص فى مستوى البوتاسيوم فى مخ الفئران. وكذلك يؤدى إلى زيادة نسبية فى الزمن اللازم لبدء حدوث النوبات الصرعية وزمن بقاء الحيوانات حيه بالاضافة إلى زيادة فى نسبة حماية الحيوانات من الموت بعد حقن مادة حامض الكاينيك (٢٥%).

- أيضاً فإن هذه الدراسة أثبتت أن حقن مادة فالبروات الصوديوم بمفردها قد أدى إلى زيادة نسبية فى الزمن اللازم لظهور النوبات التشنجية للفئران وزمن بقاء الحيوانات حيه عقب حامض الكاينيك هذا بالاضافة إلى زيادة فى نسبة حماية الحيوانات من الموت بنسبة ٥٠%. وقد كانت هذه التأثيرات المضادة للتشنج مصحوبة بزيادة فى مستوى الصوديوم فى مصل الفئران ونقص فى مستوى الصوديوم والكالسيوم وزيادة فى مستوى البوتاسيوم فى المخ.

وعند الحقن المشترك لعقارى النفيديبين وفالبروات الصوديوم أدى ذلك إلى حماية كل حيوانات التجارب من الموت المحدث بحامض الكاينيك مع زيادة فى الزمن اللازم لبدء حدوث النوبات التشنجية وكان هذا التأثير مصحوباً بنقص فى مستوى الصوديوم والكالسيوم وزيادة فى مستوى البوتاسيوم فى مخ الفئران.