RESEARCH ARTICLE

EFFECT OF AMLODIPINE ON THE ANTIEPILEPTIC ACTION OF LAMOTRIGINE, GABAPENTIN & TOPIRAMATE ON MAXIMAL ELECTROSHOCK INDUCED SEIZURES IN MICE

Background: The development of newer classes of antiepileptic drugs has created several opportunities for the treatment of epilepsy.
Aims & Objective: The present study was designed to assess the effect of amlodipine on the antiepileptic action of lamotrigine, gabapentin and topiramate in the mouse maximal electroshock-induced seizure model.
Materials and Methods: 300 Adult male mice were divided into 8 groups: (1) control to determine CS50; (2) amlodipine at doses of 5 mg/kg, 10 mg/kg and 20 mg/kg; (3) to determine ED50 of lamotrigine alone; (4) to determine ED50 of lamotrigine after amlodipine; (5) to determine ED50 of gabapentin alone; (6) to determine ED50 of gabapentin after amlodipine; (7) to determine ED50 of topiramate alone; (8) to determine ED50 of topiramate after amlodipine.
Results: It was found that amlodipine (up to 20 mg/kg), did not affect the electroconvulsive threshold in mice thus, it has no anticonvulsant effect. Moreover, amlodipine at doses of 10 and 20 mg/kg significantly enhanced the antiseizure action of the three anti convulsant drugs. Amlodipine through the blockade of N- and P/Q type calcium channels enhances the effects of lamotrigine related to the reduction of glutamate release from neurons. It binds to the alpha2 sigma subunit of voltage gated calcium channels, this may explain the observed interaction between gabapentin and amlodipine in the maximal electroshock-induced seizures in mice. Topiramate inhibits voltage-dependent sodium and L-type calcium channels. Its effect on calcium channels may explain the interaction with amlodipine.
Conclusion: Amlodipine potentiates the anticonvulsant action of lamotrigine, gabapentin and topiramate.
Key Words: Amlodipine; Seizure; Electroshock; Threshold

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INTRODUCTION

Overwhelming evidences indicate that calcium ions (Ca^{2+}) play an essential role in the pathophysiology of epilepsy. A decrease in the extracellular calcium concentrations occurs prior to onset of seizure activity followed by an increase in the intracellular calcium concentrations.[1] Generally, it is thought that the blockade of high voltage-activated (L-, N-, P/Q-type) calcium channels is associated with control of partial seizures with or without secondary generalization.[2] Some calcium channel antagonists reduce the incidence of seizures and possess anticonvulsant properties in various experimental seizure models.[3] There is no doubt that a reduced release of excitatory transmitters, including glutamate, is one of consequences of calcium channel blockade.[4] It is widely accepted that the maximal electroshock-induced seizure test is the best experimental animal model allowing for the preselection of drugs that are effective in suppression of generalized tonic-clonic seizures and, to ascertain extent, of partial seizures with or without secondary generalization.[5]

The present study is designed to study the effects of amlodipine on the threshold of electroconvulsions and on the anticonvulsant activity of lamotrigine, gabapentin and topiramate on the maximal electroshock-induced seizure model in mice.

MATERIALS AND METHODS

Animals

300 Adult male mice each weighing 20–30 gm were kept in cages with free access to food and tap water under standardized housing conditions in pharmacology department, faculty of medicine, Sebha university.

Drugs

Amlodipine besylate (AML) powder, (Pfizer co.); Gabapentin (GBP) powder, (Pfizer co.); Lamotrigine (LTN) powder, (GalaxoSmith kline co.); Topiramate (TOP) powder (Janssen-Cilag co.). All the above drugs were dissolved in distilled water and administered intraperitoneally (IP) in a volume of 5 ml/kg of body weight. Fresh drug solutions were prepared and administered in the following order: amlodipine (120min); lamotrigine (60 min)[6]; .gabapentin (30

min)[7]; and topiramate (30 min) before electro-shocks[8].

Method of Induction of Convulsions

The apparatus used is rodent shocker type 221 (Harvard apparatus GmbH Germany) with following specificity: (i) Stimulus frequency: Corresponds to supply frequency, 50 or 60 Hz; (ii) Stimulus duration: 0.1 – 9.9 sec, selected in 0.1 sec steps; (iii) Stimulus energy: 75 Watt max; (iv) Output: 0 – 300 mA, 0 – 150 mA, 0 – 100 mA, selected for voltage limits of 250 Volt, 500 Volt, 750 Volt.

Procedure: A 50 Hz stimulus of 200 msec duration was applied through saline wet ear electrodes. Current intensity was varied in step-wise manner from 1 to 30 mA to reach the current which cause convulsions without death of the animals. The current that produced convulsions with tonic hind limb extension was 13 mA. This current was used throughout this study. Observations were made to the occurrence of convulsions with tonic hind limb extension following electroshock applied to the mice.

Maximal Electro-Convulsions

The criterion for the occurrence of seizures activity was the tonic hind- limb extension (i.e. the hind limbs of animals outstretched 180° to the plane of the body axis). In this experiment two experimental models of maximal electro-convulsions were used:

(i) *Maximal Electroshock-Induced Seizure Threshold Test:* To evaluate the threshold for maximal electro-convulsions at least 4 groups of mice consisting of 10 animals per group were challenged with electroshocks of various current intensities ranging between 5 and 9 mA[6] to yield seizures in 10–30 %, 30–50 %, 50–70 %, and 70–90 % of animals consequently, then a current intensity vs. response curve was constructed, according to a log probit method by Litchfield and Wilcoxon, 1946[9] from which a

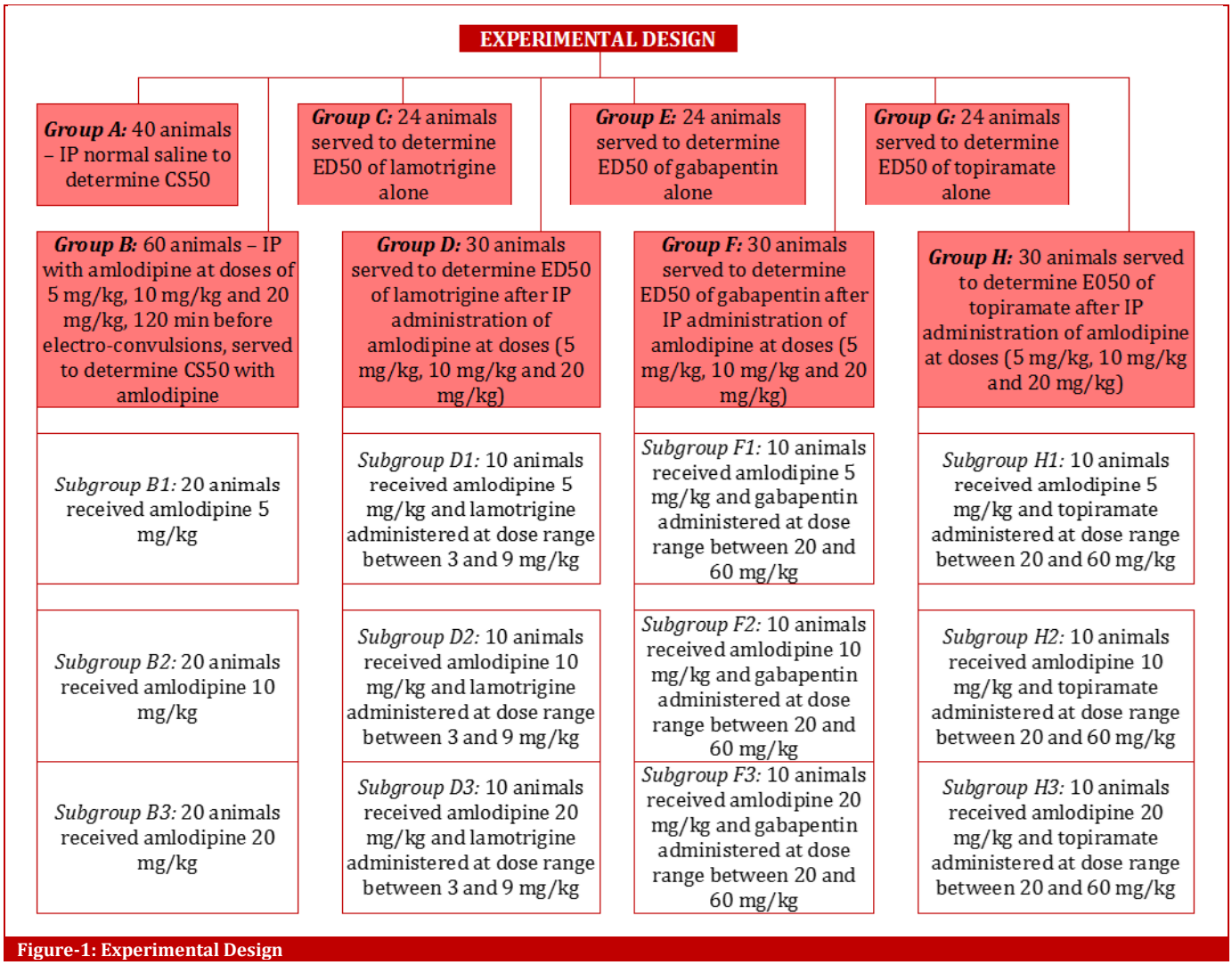

Figure-1: Experimental Design

median current strength (CS50 in mA) was calculated. Each CS50 value represents the current intensity required to induce tonic hind-limb extension in 50% of the mice challenged. After administration of a single dose of amlodipine to 4 groups of animals the mice were subjected to electro-convulsions (each group with a constant current intensity ranging between 5 - 9 mA), the threshold for maximal electro-convulsions was recorded for 3 different doses of amlodipine (5, 10 and 20 mg/kg).

(ii) *Maximal Electroshock-Induced Seizure Test:* The anticonvulsant activity of lamotrigine, gabapentin and topiramate was determined as their median effective dose (ED50 value in mg/kg) against maximal electroshock-induced seizures (0.2 sec stimulus duration and fixed current intensity of 13 mA). The animals were administered with different drug doses so as to obtain a variable percentage of protection against maximal electro shock seizures by the construction of dose-response curves for each of the tested drugs (lamotrigine, gabapentin and topiramate) administered alone, according to Litchfield and Wilcoxon. The ED50 value represents the dose of a drug required to prevent convulsions in half of the animals tested against maximal electroshock seizures. The anticonvulsant activity of lamotrigine, gabapentin and topiramate co-administered with the calcium channel antagonist (amlodipine), was evaluated and expressed as ED50.

In the present study lamotrigine was administered at dose range between 3 and 9 mg/kg [6]. Gabapentin and topiramate were administered at dose range between 20 and 60 mg/kg.[7]

Experimental Design (Figure 1)

Data Analysis

Data were entered in SPSS (Statistical Package for Social Science) for Windows version 10, checked and analysed using ANOVA (Analysis Of Variance).[10] $P < 0.05$ significant. Both, CS50 and ED50 values with their 95% confidence limits were calculated by computer log-probit analysis according to Litchfield and Wilcoxon.[6] Subsequently, the respective 95% confidence limits were transformed into standard errors (SE).[11] Statistical analysis of the data from electroconvulsive tests was performed by one-way analysis of variance (ANOVA) followed by the post-hoc Least significant difference (L. S. D.) test for multiple comparisons.[12] Differences among values were considered statistically significant if $p < 0.05$.

RESULTS

Effect of Amlodipine on the Threshold of Maximal Electro-Shock Induced Convulsions (Table 1)

The threshold for maximal electro-convulsions was determined by the current intensity required to induce tonic hind-limb extension in 50 % of animals (CS50 in mA), it was calculated as (7.1 ± 0.331 mA). Intraperitoneal administration of amlodipine at doses of 5, 10 and 20 mg/kg, (120 min before electro convulsions) did not significantly affect the threshold of a constant current-induced electroconvulsions in mice. The threshold was recorded to be 7.5 ± 0.353, 6.47 ± 0.205 and 7.75 ± 0.478 for the aforementioned doses respectively.

Effect of Amlodipine on the Anticonvulsant Action of Lamotrigine against Maximal Electroshock-Induced Seizure Model in Mice (Table 2)

Intraperitoneal administration of lamotrigine produced a significant anticonvulsant effect against maximal electro shock-induced seizures in mice (ED50 = 5.75 ± 0.478 mg/kg). Amlodipine administered before lamotrigine enhanced, in a dose-dependent manner, the anti-electro shock action of lamotrigine by significantly reducing its ED50 value on the maximal electroshock- induced seizures. Amlodipine at doses of 10 and 20mg/kg significantly decreased the ED50 value of lamotrigine protective dose from 5.75 ± 0.478 mg/kg to 3.75 ± 0.250 mg/kg and 1.91 ± 0.394 mg/kg respectively ($p<0.05$; Table 2) according to One-way ANOVA followed by the post-hoc Least significant difference (L. S. D.) test for multiple comparisons. Amlodipine at a lower dose of 5 mg/kg reduced the ED50 value of lamotrigine protective dose from 5.75 ± 0.478 mg/kg to 4.66 ± 0.406 mg/kg (Table 2). However, the difference was insignificant.

Effects of Amlodipine on the Anticonvulsant Action of Gabapentin against Maximal Electroshock-Induced Seizure Model in Mice (Table 3)

Intraperitoneal administration of gabapentin produced a significant anticonvulsant effect against maximal electro shock-induced seizures in mice (ED50 = 47.5 ± 1.443 mg/kg) Table 3. Amlodipine co-administered with gabapentin enhanced, in a dose-dependent manner, the anti-electro shock action of gabapentin by significantly reducing its ED50 value on the maximal electroshock induced seizures. Amlodipine at doses of 10 and 20 mg/kg significantly decreased the ED50 value of gabapentin from 47.5 ± 1.443 mg/kg to 37.5 ± 1.443 mg/kg and 35± 2.041

mg/kg respectively ($p<0.05$;Tab.3) according to One-way ANOVA followed by the post-hoc Least significant difference (L. S. D.) test for multiple comparisons .Amlodipine at a lower dose of 5 mg/kg reduced the ED50 value of gabapentin from 47.5 ± 1.443 mg/kg to 41.25 ± 1.250 mg/kg (Table 3). However, in this case the difference was insignificant.

Table-1: Effect of amlodipine on the threshold of maximal electro-shock induced convulsions in mice

Group (N = 10)	Control (CS50)	Dose of Amlodipine IP		
		5 mg/kg	10 mg/kg	20 mg/kg
Mean ± SE	7.1± 0.331 AB	7.5± 0.353 AB	6.47 ± 0.205 B	7.75 ± 0.478 A

N = the number of animals in each group; CS 50 value represents the current intensity required to induce tonic hind-limb extension in 50% of the mice challenged; IP = intraperitoneal; Values without common subscript capital letters are significantly different in relation to each other; Mean values = means of CS50 (in mA); SE means standard error.

Table-2: Effect of amlodipine on the anticonvulsant action of lamotrigine against maximal electroshock-induced seizure model in mice

Group (N = 10)	Control Lamotrigine (ED50)	Lamotrigine + Dose of Amlodipine IP		
		5 mg/kg	10 mg/kg	20 mg/kg
Mean ± SE	5.75 ± 0.478 A	4.66 ± 0.406 AB	3.75 ± 0.250 B	1.91 ± 0.394 C

Table-3: Effect of amlodipine on the anticonvulsant action of gabapentin against the maximal electroshock-induced seizure model in mice

Group (N = 10)	Control Gabapentin (ED50)	Gabapentin + Dose of Amlodipine IP		
		5 mg/kg	10 mg/kg	20 mg/kg
Mean ± SE	47.5 ± 1.443 A	41.25 ± 1.25 B	37.5± 1.443 BC	35 ± 2.041 C

Table-4: Effect of amlodipine on the anticonvulsant action of topiramate against maximal electroshock-induced seizure model in mice

Group (N = 10)	Control Topiramate (ED50)	Topiramate + Dose of Amlodipine IP		
		5 mg/kg	10 mg/kg	20 mg/kg
Mean ± SE	52.5 ± 1.443 A	48.75± 2.393 AB	42.5 ± 3.227 B	33.75± 1.250 C

Effects of Amlodipine on the Anticonvulsant Action of Topiramate against Maximal Electroshock-Induced Seizure Model in Mice (Table 4)

Intraperitoneal administration of topiramate produced a significant anticonvulsant effect against maximal electro shock-induced seizures in mice (ED50 = 52.5 ± 1.443 mg/kg) Table 4. Amlodipine co-administered with topiramate enhanced, in a dose-dependent manner, the anti-electroshock action of topiramate by significantly reducing its ED50 value in the maximal electroshock induced seizures. Amlodipine at doses of 10 and 20mg/kg significantly decreased the ED50 value of topiramate from 52.5 ± 1.443 mg/kg to 42.5 ± 3.227 mg/kg and 33.75± 1.250 mg/kg respectively ($p<0.05$;Tab.4) according to One-way ANOVA followed by the post-hoc Least significant difference (L. S. D.) test for multiple comparisons . Amlodipine at a lower dose of 5 mg/kg reduced the ED50 value of topiramate from 52.5 ± 1.443 mg/kg to 48.75± 2.393 mg/kg (Table 4). However, in this case the difference was insignificant.

DISCUSSION

The trials for epilepsy treatment have increased in the last decade with the introduction of several new antiepileptic drugs e.g. lamotrigine , gabapentin and topiramate.[13] The present study was designed to assess the effect of amlodipine (a calcium channel blocker) on the antiseizure protective action of lamotrigine, gabapentin and topiramate against maximal electroshock-induced seizure model in mice. It was found that amlodipine (up to 20 mg/kg) did not affect the electroconvulsive threshold in mice and this finding is partially in agreement with those documented earlier by Kaminski et al,1999.[14] However, amlodipine at doses of 10 and 20 mg/kg significantly enhanced the antiseizure action of lamotrigine. This enhancement appeared at much higher doses than in the case of the conventional antiepileptic drugs. This finding is partially in agreement with Jarogniew et al, 2007.[2] Amlodipine at a dose of 5 mg/kg potentiated the anticonvulsant action of carbamazepine, phenobarbital and valproate, but not that of phenytoin in the maximal electroshock-induced seizures in mice.[14] In the present study, it is noteworthy that the ED50 values of the anti-epileptic agents each administered alone and in combination with amlodipine were statistically analyzed and compared by one-way ANOVA (analysis of variance) followed by the post-hoc L.S.D (Least significant difference) test for multiple comparisons. In contrast, the results presented in the previous studies were compared separately to their control ED50 values using log-probit method only.[3] Quite recently, it has been documented that statistical analysis of data obtained from log-probit method should be performed by one-way ANOVA followed by the post-hoc test for multiple comparisons and this method has gained priority over statistical analysis with log-probit method only.[5] Regarding the antiepileptic effect of lamotrigine, the results of the present study are in agreement with Messenheimer (1995)[15] who stated that the drug mechanism of action against partial tonic-clonic and secondary generalized seizures is by blockade of voltage dependent sodium channels which stabilize pre-synaptic membranes and inhibit excitatory neurotransmitter release. Also in some double-blind placebo-controlled trials, lamotrigine was effective in treating simple or complex partial seizures

with or without secondary generalized tonic-clonic seizures. Moreover, there is evidence of improvement in patients with primary generalized seizures and in children with multiple seizure types.[16]

The results of the present study regarding the antiepileptic effect of lamotrigine are in accordance with the results of De-Sarro et al. (1996)[17] who studied the effect of intraperitoneal administration of lamotrigine (0.5–10 mg/kg) on audiogenic seizures (sound induced) in mice and demonstrated that lamotrigine was able to antagonize the audiogenic seizures in a dose-dependent manner. It is also in agreement with Martinovic (2004)[18] who demonstrated the efficacy of lamotrigine in patients with epilepsy. Martinovic noticed that lamotrigine had a significant antiepileptic long-term efficacy and improved the seizures in 55.3% of the patients.

The mechanisms of the antiepileptic action of lamotrigine had been demonstrated by Cheung et al. (1992)[19] who stated that the anticonvulsant action of lamotrigine is mainly due to its effect on voltage-sensitive sodium channels and recently by Ahmad et al. (2004)[20] who stated that its action is mainly due to the reduction of glutamate release which results from inhibition of Na+ channels and stabilization of neuronal membranes.On the other hand our findings are in contradiction to those reported by Gasior et al. (1999)[21] who stated that lamotrigine in normal therapeutic doses is ineffective in cocaine induced seizures in mice. This contradiction may be due to the mechanism of cocaine induced seizures which depends mainly on blockage of GABA receptors. Another finding of the author is that large doses of lamotrigine may produce status epilepticus. This may be due to an unexplained interaction with cocaine. However, in-vitro studies demonstrated that lamotrigine reduce the release of GABA in the cerebrocortical slices of rats in doses higher than that required to reduce release of glutamate and aspartate.[22]

To explain the interaction between lamotrigine and amlodipine against the maximal electroshock-induced seizure test, one should consider molecular mechanisms of action of both drugs. As regards the anticonvulsant effect of lamotrigine, it has been documented that the drug acts at voltage-dependent sodium channels to decrease the presynaptic release of the excitatory neurotransmitter glutamate.[19] Lamotrigine blocks the release of endogenous glutamate. Moreover, lamotrigine decreases voltage-gated calcium currents[23] and this effect, probably, contributes to a decrease in glutamate release. On the other hand, experimental evidence indicates that N-type calcium channels are responsible for glutamate release in the cerebral cortex and hippocampus.[24] Amlodipine belongs to the 1, 4-dihydropyridine class of calcium channel antagonists.[25] It blocks N- and P/Q-type calcium channels showing high affinity for both these channels.[26] We can suggest that amlodipine through the blockade of N- and P/Q type calcium channels enhances the effects of lamotrigine related to the reduction of glutamate release from neurons. This hypothesis can readily explain the observed interaction between lamotrigine and amlodipine in the maximal electroshock-induced seizures in mice. Regarding the anti-epileptic effect of gabapentin, the present study is supported by the findings of Mclean (1995)[27] who studied the effect of gabapentin on the maximal electroshock test in animal models. The author reported that gabapentin was as potent as phenytoin and this is explained by the possibility of enhancing the ratio of gamma-aminobutyric acid / glutamate, ion-channel actions, and/ or enhancement of nonsynaptic GABA release.

The present study is also consistent with the work of Watson et al. (1997)[28] who stated that gabapentin (50 or 100 mg/kg) decreased the convulsive response to the audiogenic stimuli during the withdrawal period of ethanol in mice which may be due to the increase in GABA level produced by gabapentin. The antiepileptic effect of gabapentin had been studied by Gasior et al. (1999)[21] who demonstrated that gabapentin administered in a dose range from 10 to 100 mg/kg produced dose dependent almost full protection against cocaine induced seizures in mice. Cocaine induced seizures occur as a result of a direct inhibitory effect of cocaine on the GABAA receptor-mediated chloride current in hippocampal neurons and/or enhanced dopaminergic neurotransmission which can enhance the release of glutamate. Drugs which enhance GABA-mediated neuronal inhibition offer the best protective effect against cocaine-induced seizures whereas antagonists of N-methyl-D-aspartate (NMDA) receptors are less effective.[29] Our findings are also supported by the suggestion of Rizwan et al. (2003)[30] who studied the effect gabapentin on pentetrazole-induced convulsions in mice and noticed that gabapentin led to marked reduction in seizure activity and attributed this effect to the facts that gabapentin increases GABA levels in the brain within 30–60 minutes after its administration and also gabapentin is a putative inhibitor of glutaminergic system.[31] Our results are also in agreement with the results of the clinical study of Zhu et al. (2005)[32] in

patient with refractory partial epilepsy. The authors demonstrated that the new antiepileptic drug gabapentin decreased the duration of seizures by 75%.

To explain the appearance of the favorable interaction between gabapentin and amlodipine in the maximal electroshock-induced seizure test, Gabapentin increases the release of several monoamine neurotransmitters (e.g. norepinephrine) and inhibits glutamate synthesis by branched-chain amino acid aminotransferase.[33] It also may modulate Ca++ channels.[34] It binds to the alpha2 sigma subunit of voltage gated calcium channels.[7]

It is worth reminding that topiramate is an antiepileptic drug sharing multiple mechanisms of action. This antiepileptic drug inhibits voltage-dependent sodium and L-type calcium channels[35], potentiates GABA-mediated inhibitory neurotransmission through binding to a novel site on the GABAA-receptor complex[36] and reduces excitatory neurotransmission by blocking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate subtypes of glutamate receptors.[11] Topiramate is also an inhibitor of several carbonic anhydrase (CA) isozymes especially CA-II and CA-IV.[37] Its effect on calcium channels may explain the interaction with amlodipine.

Studies carried out so far have established that topiramate is highly effective in the maximal electroshock test and relatively weak against pentylenetetrazol-induced seizures.[37] There are data indicating that the bicarbonate ion can induce depolarization at the moment GABAA channels have been opened by GABA.[38] This effect can be decreased by a carbonic anhydrase inhibitor which may explain the anticonvulsant activity of topiramate. The available data indicates that blockage of voltage-dependent Na+ channels as the mechanism underlying the anticonvulsant activity of topiramate is also the mechanism of some of the conventional antiepileptic drugs such as diphenylhydantoin, carbamazepine and valproate.[39] The potentiation of GABA-ergic inhibition exhibited by topiramate is, in turn, found with valproate, barbiturates and benzodiazepines.[38] Furthermore, there is an increasing evidence that several of the basic drugs may also affect glutamatergic excitation.[8] It may be concluded, therefore, that the anticonvulsant activity of topiramate is mostly due to a combination of the mechanisms responsible for the anticonvulsant effect of the older antiepileptic drugs.[31]

The present study was designed to assess the effect of amlodipine on the protective action of lamotrigine, gabapentin and topiramate in the mouse maximal electroshock-induced seizure model.It was found that amlodipine (up to 20 mg/kg) did not affect the electroconvulsive threshold in mice thus it has no anticonvulsant effect. Moreover, amlodipine at doses of 10 and 20 mg/kg significantly enhanced the antiseizure action of the three anti convulsant drugs. Amlodipine through the blockade of N- and P/Q type calcium channels enhances the effects of lamotrigine related to the reduction of glutamate release from neurons. This hypothesis can readily explain the observed interaction between lamotrigine and amlodipine in the maximal electroshock-induced seizures in mice. Gabapentin increases the release of several monoamine neurotransmitters (e.g. norepinephrine) and inhibits glutamate synthesis by branched-chain amino acid aminotransferase. It also may modulate Ca++ channels. It binds to the alpha2 sigma subunit of voltage gated calcium channels. This may explain the observed interaction between gabapentin and amlodipine in the maximal electroshock-induced seizures in mice. Topiramate inhibits voltage-dependent sodium and L-type calcium channels, potentiates GABA-mediated inhibitory neurotransmission through binding to a novel site on the GABAA-receptor complex and reduces excitatory neurotransmission by blocking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate subtypes of glutamate receptors. Interestingly, Topiramate is also an inhibitor of several carbonic anhydrase (CA) isozymes, especially CA-II and CA-IV. Its effect on calcium channels may explain the interaction with amlodipine.

CONCLUSION

Amlodipine potentiates the anticonvulsant action of lamotrigine, gabapentin and topiramate. If the results from this study can be extrapolated to the clinical settings, a novel therapeutic option in the management of epilepsy might be created for epileptic patients. Thus, Amlodipine deserves more attention, from a preclinical point of view, as a potentially favorable drug that could be applied in patients treated with lamotrigine, gabapentin or topiramate who additionally required a calcium channel antagonist treatment for other than epilepsy reasons.

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