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Research Article

Renin-angiotensin system inhibitors potentiate the anticonvulsant activity of valproate in the mouse pilocarpine-induced seizures model

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Abstract

Systemic inhibition of the renin-angiotensin-aldosterone system (RAAS) has been recently suggested to participate in the regulation of seizures susceptibility. The purpose of the current study was to evaluate the effect of lisinopril and valsartan as RAAS modifiers on the protective action of the antiepileptic sodium valproate (VPA) against pilocarpine-induced convulsions in mice. Male albino mice were used in the study, and were grouped into five groups, *viz.,* normal control group, seizures control group (seizures induced with pilocarpine), VPA-treated group and groups treated with combination of VPA with either lisinopril or valsartan. Lisinopril and valsartan were given orally for three (3) consecutive days including the day of seizure induction while VPA was injected in the three treatment groups 30 minutes before pilocarpine injection. All animals were observed for three (3) hours to assess the seizure severity and the latency to the onset of seizures. Death rate over the next twenty four (24) hours was recorded. Brain specimens from survivors were taken and examined pathologically. Treatment with either lisinopril or valsartan potentiated the effect of VPA in reducing the seizure severity, prolonged the onset of seizures, reduced the brain insult and decreased the mortality rate. Both agents did not influence plasma concentration of VPA excluding pharmacokinetic interactions. It is concluded that RAAS inhibition combined to VPA treatment may hold a potential for the cure of pathologies such as epilepsy.

Keywords: Epilepsy, seizures, lisinopril, valsartan, valproate, pilocarpine

INTRODUCTION

Epilepsies affect 1–3% of the world's population and are characterized by recurrent epileptic seizures that are triggered by abnormal, excessive and/or hypersynchronous neuronal activity (Engel, 1995). The first choice of treatment for epilepsy is drug-based, and approx. 70% of the anticonvulsants are described to be effective. Hence approximately 30% of the epileptic population is non responsive to classical anticonvulsants, which are also known to yield a panel of severe side effects, including neurotoxicity (Elger and Schmidt, 2008).

Based on clinical practice, valproic acid (VPA) is usually used in the treatment of generalized, partial, and absence (petit mal) seizures. As such, it has the widest spectrum of activity compared to the other currently available antiepileptic drugs (Duncan et al., 2006). Although the precise mechanism of action for VPA is unknown, its antiepileptic effect is thought to result from its ability to increase concentrations of the neuroinhibitor γ-aminobutyric acid (GABA), to potentiate the postsynaptic response to GABA, or to exert a direct effect on cellular membranes.

The renin–angiotensin aldosterone system (RAAS), acting mainly through the peptide angiotensin II (AngII), is classically involved in blood pressure regulation and water–electrolyte balance (Oliveira et al., 2007). Beside the peripheral system, all components (precursors and enzymes) of RAAS are expressed in the Brain (Wright and Harding, 1997)

where it has been mostly associated with the regulation of homoeostatic processes, such as thirst, hormone secretion and thermoregulation (Paul et al., 2006). Additionally, the brain RAAS seems to be implicated in stress, anxiety, depression, cognition, and epilepsy (Kumaran et al., 2008; Tchekalarova and Georgiev, 2005; Wright et al., 2008). AngII exerts its actions through its receptors in different brain areas (deGasparo et al., 2000). A number of these areas including the hippocampus and amygdala are involved in seizure susceptibility regulation (Jefferys, 1998). Indeed, a study reported that RAAS components were up-regulated in the brain of patients with temporal lobe epilepsy (TLE) (Arganaraz et al., 2008) which prompted many researchers to investigate a possible role for the angiotensinergic pathway in epilepsy.

Interestingly, previous experimental research work revealed that the result of ACE inhibition in different models of epilepsy is not necessarily the same; captopril was able to protect mice against convulsions induced by strychnine, although the same drug was ineffective in bicuculline-induced seizures in mice (Minano et al., 1987). Regarding potentiating effects of classical antiepileptic drugs (AEDs), captopril has shown in one study to enhance the anticonvulsant activity of carbamazepine and lamotrigine against maximal electroshock-induced seizures in mice (Lukawski et al., 2010a). In a second study, enalapril was able to enhance the protective effects of valproate (Lukawski et al., 2011). Thus, it is conceivable that the use of such ACE-inhibitors might influence the efficacy of some AEDs. Taking into consideration, the significant role of RAAS in brain, we sought to evaluate the influence of the ACE inhibitor, lisinopril and that of the selective AT_1 receptor blocker, valsartan on the protective action of the classical AED valproate. Pilocarpine-induced seizures model in mice has been employed since pilocarpine is a chemoconvulsant established to induce an animal model of TLE (Shibley and Smith, 2002) the highest prevalent type of seizures in humans (Fisher et al., 1998). It has been demonstrated that epileptic insults induced by pilocarpine produce various cellular and molecular alterations consistent with TLE (McNamara et al., 2006).

MATERIAL AND METHODS

Animals

Male albino mice weighing 20-25 g were used. Animals were purchased from the animal house (National Research Center, Egypt) and housed in groups of six to eight (6-8) in colony cages at room temperature, under a 12-h light/12-h dark cycle with food pellets and water available ad libitum. Control animals were always tested on the same day as the respective experimental groups. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

Experimental Design

Procedures involving animals and their care were conducted in conformity with national law and policies and approved by the Local Ethics Committee for Animal Experiments. Five experimental groups, each consisting of twenty (20) mice, were allocated according to a randomized schedule, and each mouse was used only once. One group was intraperitoneally injected with saline and served as normal control group. Group two (2) received pilocarpine (250 mg/kg, i.p.) and served as seizures control group. Groups three (3), four (4) and five (5) were respectively treated with sodium valproate (VPA) (250 mg/kg, i.p.) alone and in combination with lisinopril (20 mg/kg) or valsartan (20 mg/kg) before induction of seizure with pilocarpine. Lisinopril and valsartan were given orally for three (3) consecutive days including the day of seizure induction while VPA injected in the three treatment groups thirty (30) minutes before pilocarpine injection. Dose of VPA was documented to correspond to its ED_{50} inpilocarpine model in mice (Lukawski et al., 2010b)

Behavioral evaluation of motor seizure activity

All animals were observed for 3 hours to record the spontaneous recurrent behavioral seizures those were scored using the Racine scale (Ben Ari, 1985; Del-Bel et al., 1997). This scale classifies seizures to fall into any of classes 0-5 as follows:0 = immobility with open eyes, 1 = facial convulsions and or “wet dog shakes”, 2 = same behaviors as class 1 with head nodding, 3 =unilateral/bilateral forelimb clonus with a lordotic posture 4 = bilateral forelimb clonus continued along with rearing, and 5 = same behaviors as class three (3) and four (4) seizure but more generalized convulsions and falling.The time in minutes from pilocarpine administration to the first appearance of seizure activity was measured for each animal(seizures onset). The mortality rate among each group over a period of 24 hours was recorded.

Histopathological Study

Survivors from different groups were killed, whole brain excised and lightly washed with saline. Autopsy samples were taken from the brain specimens and fixed in 10% formol saline for histopathological examination according to

Banchroft et al. (1996). Dehydration with alcohol was achieved then specimens were embedded in paraffin bees wax tissue blocks which were then sectioned at 4 microns by the microtome. The obtained tissue sections deparaffinized and stained by hematoxylin and eosin stains then examined through the electric light microscope. A single blind design is followed for the histopathological study to avoid the bias of the pathologist.

Estimation of plasma concentrations of valproate

Mice (20–28 g) were given either VPA alone or one drug (lisinopril or valsartan) plus VPA. Drugs were administered i.p., lisinopril (20mg/kg) or valsartan (20 mg/kg) 60 minutes before plus VPA forty five (45) minutes before drawing the blood samples. Mice were killed by decapitation and blood samples of approximately 1ml were collected into heparinized Eppendorf tubes. VPA total plasma concentrations were estimated by the LC-MS technique according to Tang et al. (1999). The VPA concentrations were expressed in µg/ml of plasma.

Statistical analysis

Continuous data were expressed as means ±SD. Number of animals was from twelve (12) to twenty (20) for the *in vivo* experiments while it was five to seven (5-7) for kinetic analysis. Statistical analysis was performed using Chi square test for seizure severity score and student t-test for the onset time of seizure. For the kinetic study, ANOVA was applied followed by Tukey-Kramer multiple comparison test in case of significance detection. Differences between means were considered significant at $p < 0.05$.

RESULTS

As demonstrated in figure 1, results of the present study revealed a clear enhancement of the anticonvulsant effects of valproic acid when combined with either lisinopril or valsartan in the pilocarpine-induced seizure model in mice. Seizure severity score according to Racine scale (0-5) showed that pilocarpine induced high severity seizures as about 60% of animals showed scale of 4 or 5 severity.

Treatment with valproic acid (VPA) significantly reduced the number of animals showing high scores (4 and 5) of seizures (30% for VPA group as compared to 61.9% for pilocarpine group) and shifted them to lower scores (figure 1).

Combination of VPA with either lisinopril or valsartan potentiated its protection effect as reflected by more animals being shifted to lower score seizures especially with valsartan which resulted in 0% of animals showing score three (3) or four (4). Moreover, complete protection from pilocarpine-induced seizures was demonstrated in some animals upon adding either of the RAAS modifiers to VPA treatment. Hence 10% while 30% of animals showed a seizure score of 0 (which means showed no convulsions) with lisinopril and valsartan respectively (figure 1).

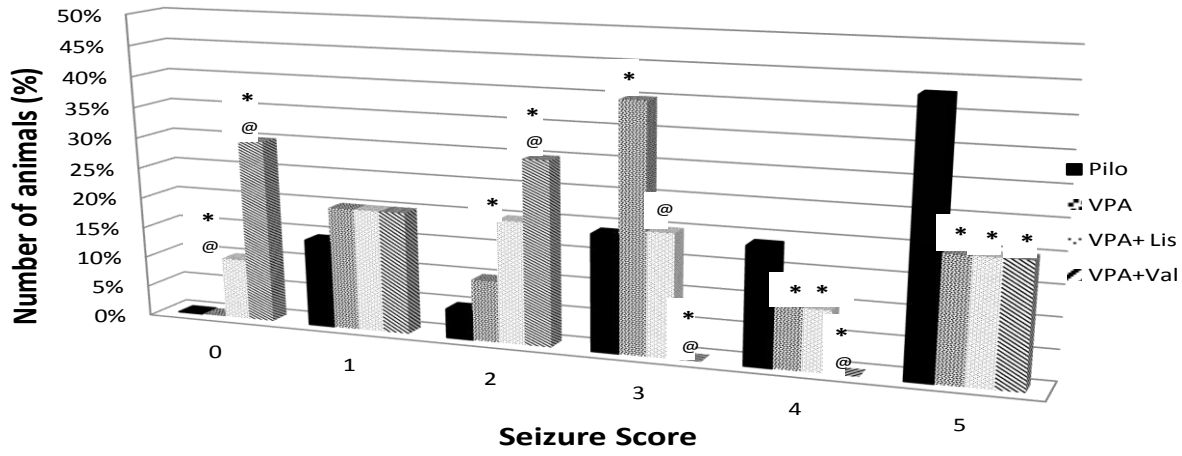


Figure 1. Seizure severity score according to Racine scale (0-5) measured in mice of the seizure control group treated intraperitoneally with 250 mg/kg of pilocarpine (Pilo) and in mice protected with either 250mg/kg of valproic acid (VPA) alone or in combination with lisinopril 20mg/kg/day (VPA + Lis) or with valsartan 20mg/kg/day (VPA + Val). Means of results from 12-20 animals were calculated.
* indicates significant from seizure control group receiving pilocarpine
@ indicates significant from VPA-treated group. Significance is considered at $p < 0.05$.

Concerning the onset time to seizures, it was increased by 64.28% and by 70.5% with lisinopril and valsartan respectively as compared to treatment with VPA alone (results shown in figure 2). Treatment with VPA alone increased the onset time as compared to seizure control group but this increase was non-significant.

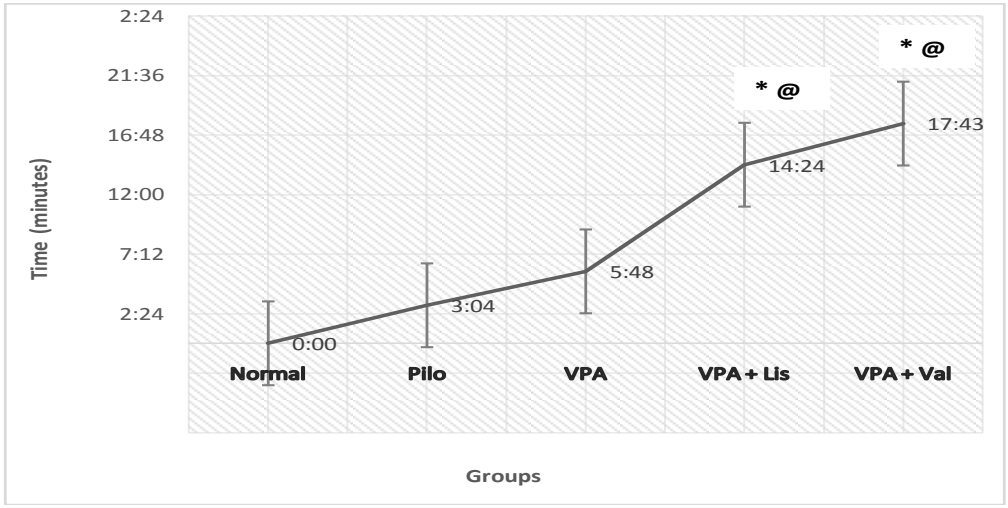


Figure 2. Onset time (in minutes) to seizures measured in mice of the seizure control group treated intraperitoneally with 250 mg/kg of pilocarpine (Pilo) and in mice protected with either 250mg/kg of valproic acid (VPA) alone or in combination with lisinopril 20mg/kg/day (VPA + Lis) or with valsartan 20mg/kg/day (VPA + Val). Means of results from 12-20 animals were calculated.
* indicates significant from seizure control group receiving pilocarpine
@ indicates significant from VPA-treated group. Significance is considered at $p < 0.05$.

Figure 3 showed that combination of VPA with either RAAS modifiers did not significantly improve the death rate (30% for both drugs combined with VPA and 20% for VPA alone). However, all the three treatment groups had markedly lower the percentage of death among their groups as compared to the control group receiving no treatment (52.63%).

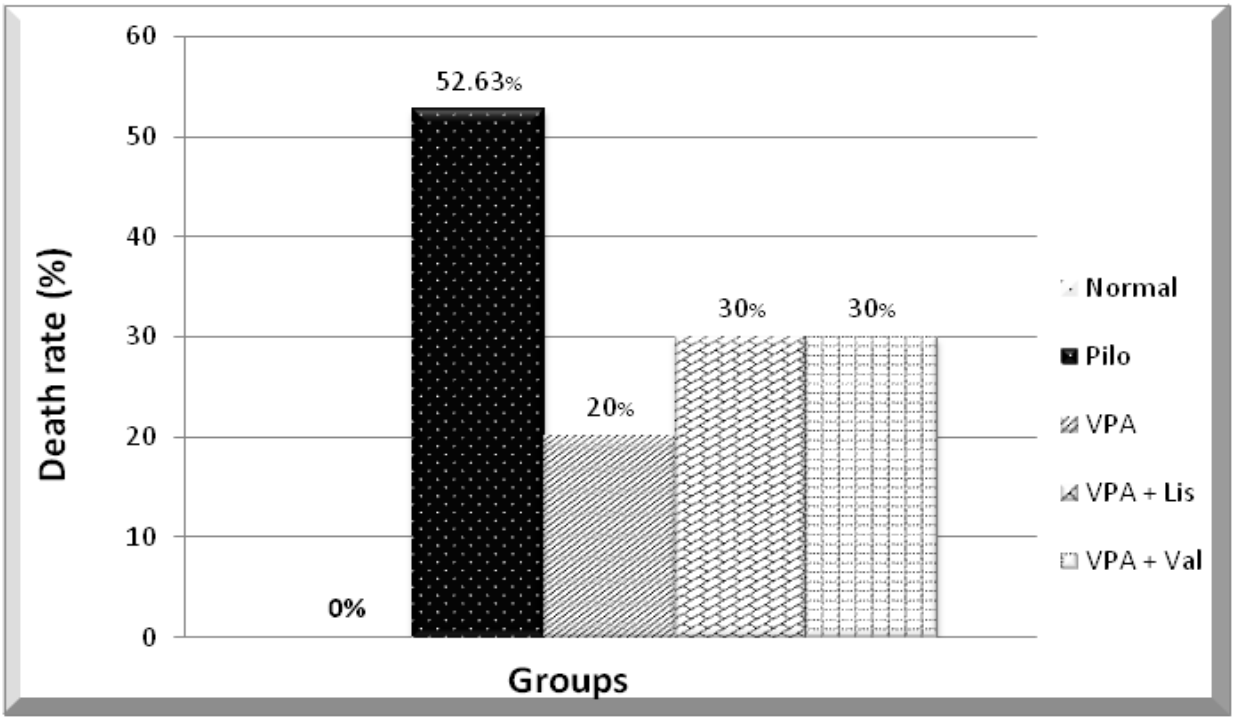


Figure 3. Percentage of death measured 24 hours after induction of seizures among groups of mice of the seizure control group treated intraperitoneally with 250 mg/kg of pilocarpine (Pilo) and in mice protected with either 250mg/kg of valproic acid (VPA) alone or in combination with lisinopril 20mg/kg/day (VPA + Lis) or with valsartan 20mg/kg/day (VPA + Val). Means of results from 12-20 animals were calculated.
* indicates significant from seizure control group receiving pilocarpine
@ indicates significant from VPA-treated group. Significance is considered at $p < 0.05$.

Regarding the results of the histopathological examination, focal gliosis in the cerebral cortex and congestion in the cerebral blood vessels were observed in the brain specimens isolated from pilocarpine group (figure 5) as compared to normal brain specimens (figure 4).In the seizure control group, the hippocampus also showed atrophy

with gliosis in between the degenerated neuronal cells as well as focal haemorrhage. Treatment with VPA alone or combined with lisinopril or with valsartan markedly reduced the deterioration of the brain histologically as clearly demonstrated in figures 6, 7 and 8 as well as in table 1.

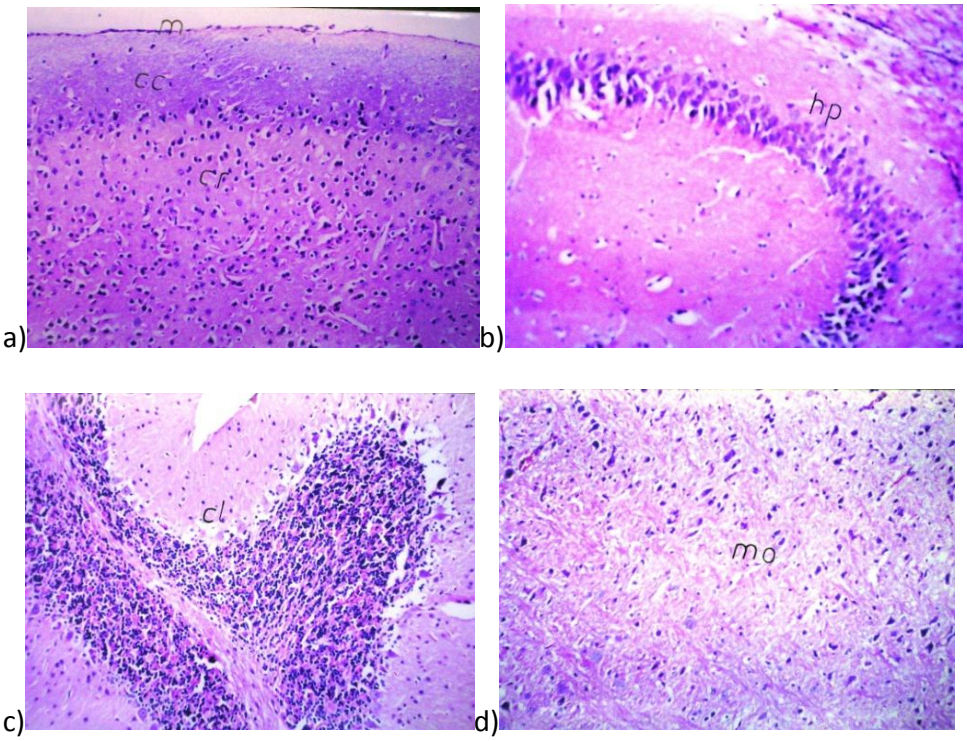


Figure 4. Histopathology of normal brain specimens. No histopathological alteration observed in the meninges, cerebral cortex, cerebrum, hippocampus, cerebellum and medulla oblongata. Specimens were examined with hematoxylin and eosin.

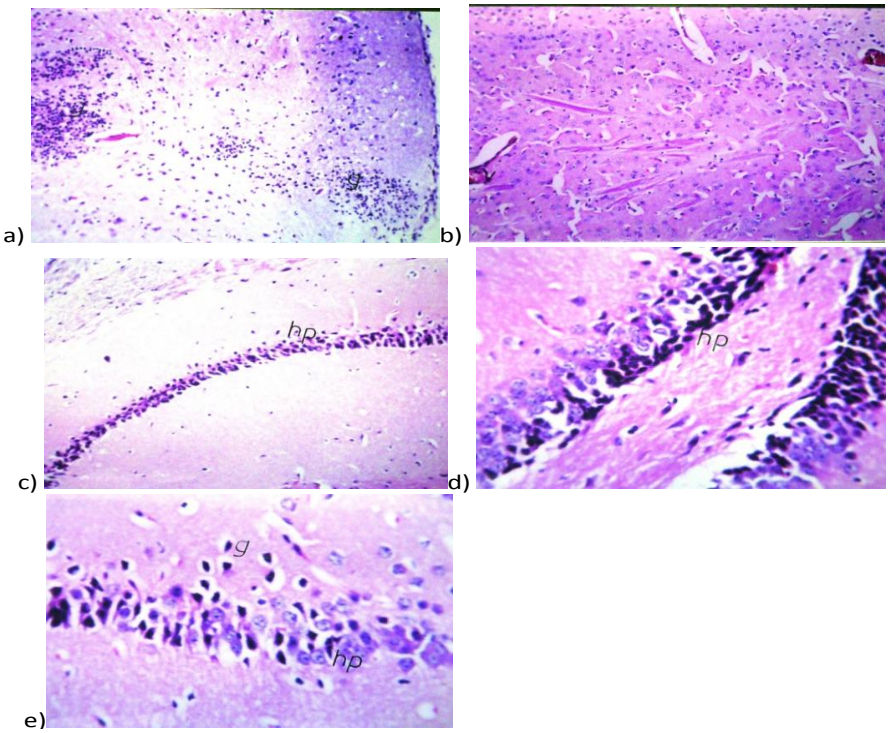


Figure 5. Histopathology of brain specimens from mice in which seizures were induced by pilocarpine 250 mg/kg, i.p. Focal gliosis was detected in the cerebral cortex and cerebrum (a), associated with congestion in the cerebral blood vessels (b). The hippocampus showed atrophy with gliosis in between the degenerated neuronal cells (c and d) as well as in the pyramidal cells (e). Specimens were examined with hematoxylin and eosin.

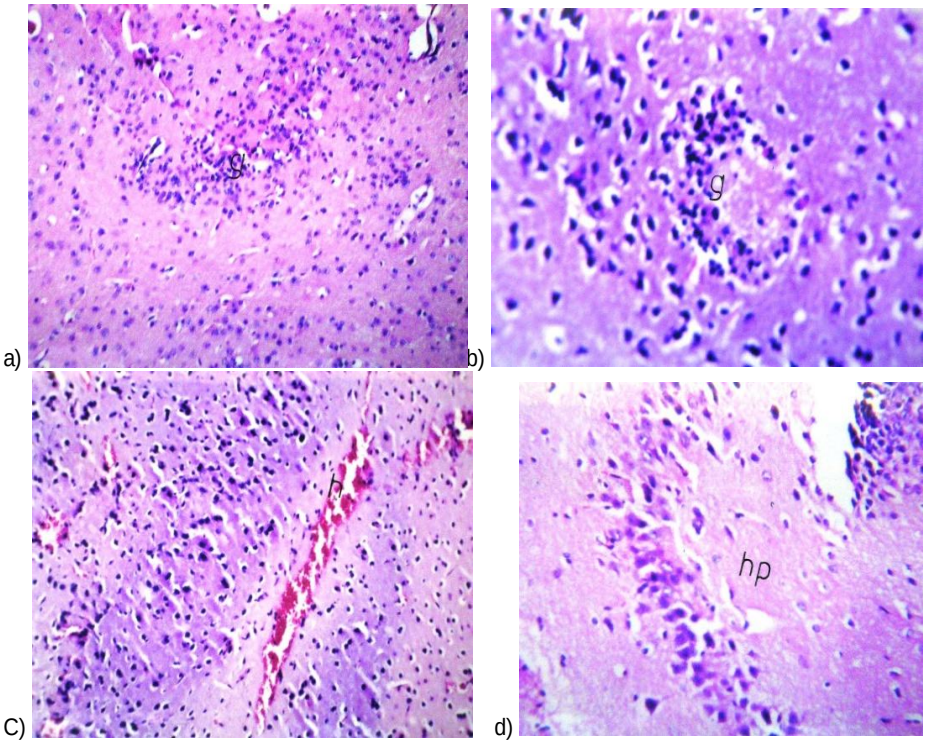
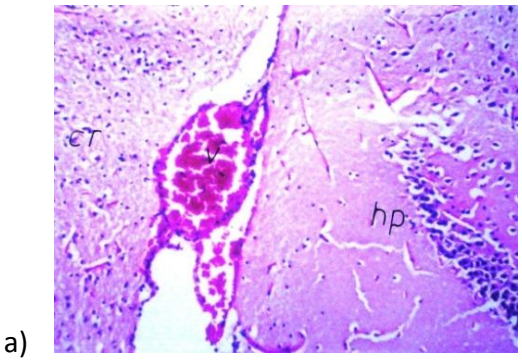


Figure 6. Histopathology of brain specimens from mice in which seizures were induced by pilocarpine 250 mg/kg, i.p and protected with VPA alone. The cerebrum showed focal gliosis and demyelination (a and b) associated with focal hemorrhage (c). The hippocampus was histologically intact as recorded in (d). Specimens were examined with hematoxylin and eosin



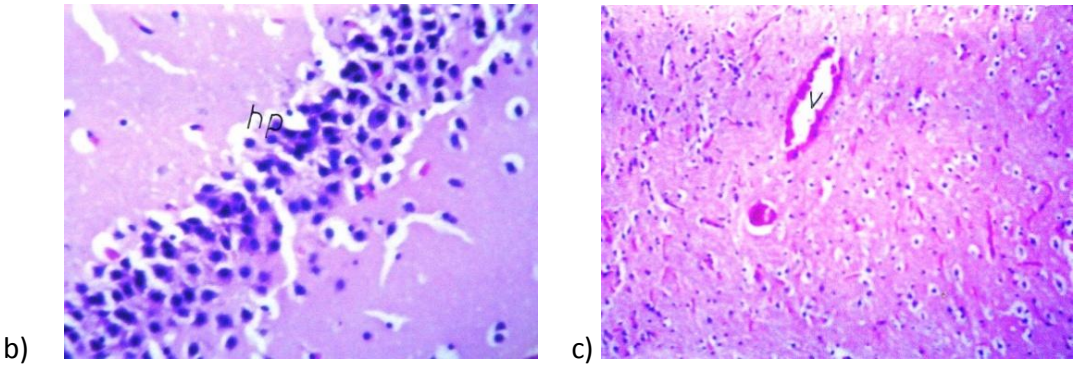


Figure 7. Histopathology of brain specimens from mice in which seizures were induced by pilocarpine 250 mg/kg, i.p. and protected with VPA + Lisinopril. Congestion was observed in the blood vessels between the cerebrum and hippocampus (a), associated with neuronal degeneration in the hippocampal neuronal cells (b). Congestion was noticed in the cerebral blood vessels (c). No focal hemorrhage in cerebrum. Specimens were examined with hematoxylin and eosin.

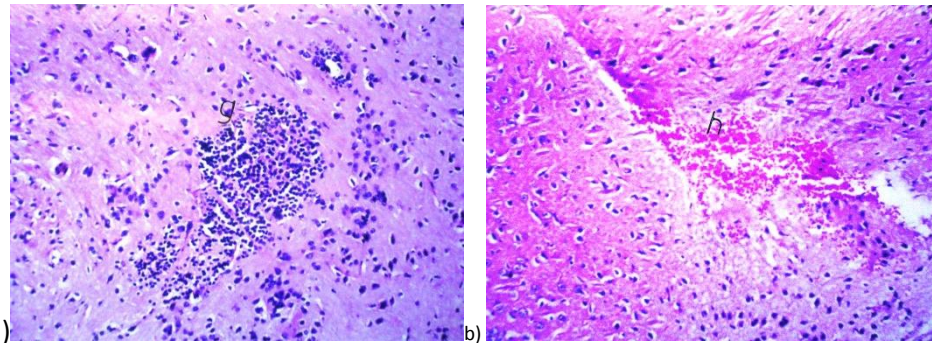


Figure 8. Histopathology of brain specimens from mice in which seizures were induced by pilocarpine 250 mg/kg, i.p. and protected with VPA + Valsartan. The cerebrum showed focal gliosis (a), as well as focal hemorrhage in the cerebrum (b). No focal hemorrhage in the hippocampus and blood vessels were not congested. Specimens were examined with hematoxylin and eosin.

Table 1. The severity of the reaction in the brain according to the histopathologic alteration in different groups

Group Histopathological Alteration	normal	Pilo	VPA	VPA + Lis	VPA + Val
Gliosis with neuronal degeneration.	---	++++	+++	+	++
Congestion in blood vessels.	---	++++	+	++	---
Focal haemorrhage in cerebrum	---	++++	++	---	+
Focal haemorrhageand /or degeneration of the hippocampus	---	++++	---	+	---

++++ Very severe, +++ severe, ++ moderate, + mild, - Nil

Table 2. Influence of Lisinopril (Lis) or valsartan (Val) on plasma level of valproic acid (VPA) in mice

Plasma VPA concentration (µg/ml)	VPA alone (mean ± SD)	VPA + Lis (mean ± SD)	VPA + Val (mean ± SD)
	171.0960 + 8.742	174.033 + 13.640	173.429 + 11.135

Drugs were administered i.p. vehicle, Lisinopril (20 mg/kg), or valsartan (20 mg/kg) 60 min before plus valproic acid 45 min before drawing the blood samples.

Determination of the plasma concentration of VPA following its administration either alone or combined with lisinopril or valsartan showed no significant difference between the three groups which revealed that neither drugs affected the kinetic parameters influencing VPA plasma concentration.

DISCUSSION

Systemic administration of pilocarpine to mice leads to epileptic injuries which include degeneration of the neuronal cells, focal gliosis in the cerebral cortex and cerebrum, and hippocampal atrophy. These findings are consistent with previous research demonstrating the criteria of pilocarpine-induced seizure model in rodents (Jeong et al., 2013). The present data indicate that the protective action of the antiepileptic drug (AED) valproate against pilocarpine-induced seizures in mice is potentiated by co-administration of the non sulfhydryl ACE inhibitor lisinopril as well as the AngII receptor blocker valsartan. The mechanism causing the observed augmentation of the potency of valproate is based on a pharmacodynamic interaction since we can exclude pharmacokinetic alterations being plasma level of valproate unchanged in the presence of either lisinopril or valsartan.

Our results are in agreement with previous data illustrating the positive role of RAAS inhibition in different model of seizures. Fosinopril and zofenopril, two ACE inhibitors, potentiated the anticonvulsant activity of antiepileptic drugs against audiogenic seizures in DBA/2 mice (De Sarro et al., 2012). Furthermore, captopril potentiated the anticonvulsant activity of carbamazepine and lamotrigine in the maximal electroshock seizure (MES) test in mice which is regarded as an experimental model of tonic-clonic seizures (Łukawski et al., 2010a). Moreover, the protective action of valproate against MES-induced seizures in mice has been demonstrated to be significantly augmented upon co-administration of either the ACE inhibitor enalapril (Łukawski et al., 2011) or the ARBs losartan and telmisartan (Łukawski et al., 2010b).

Not in accordance with our results are the studies which showed protection against experimentally-induced seizures by injection of the peptide AngII rather than RAAS inhibition (Tchekalarova and Georgiev, 1999; Tchekalarova et al., 2003). The seizures studied in the previously-mentioned studies were induced by pentylenetetrazole.

The activity of both RAAS modifiers in the present model was observed in a dose range at which a decrease in mean arterial blood pressure must be assumed. The possibility, however, that the haemodynamic effects could be of relevance forthe observed anticonvulsant properties of these agents seems very unlikely. One reason is that it is not actually logical to obtain, over the schedule of treatment in the present study, significant haemodynamic effects that had the chance to subsequently produce anticonvulsant activity. Secondly, De Sarro and co-workers, (2012) demonstrated that enalapril, which can be expected to produce significant changes of cardiovascular parameters at adequate doses, showed no clear anticonvulsant activity. So, a suggestion of a causative relation between decrease in blood pressure and protection against convulsions induced by pilocarpine is far from being an acceptable hypothesis.

The present data further suggest that the drugs used in the present study produce their potentiating effects on valproate anticonvulsant activity through central rather than peripheral effects. Indeed, the pathological study revealed a clear protection of brain tissue against pilocarpine insult which indicates that the effects of lisinopril and vlasartan are mediated at a brain level. Actually, lisinopril showed long-lasting inhibitory action on brain ACE *ex vivo* as demonstrated by Cushman et al. (1989). Regarding valsartan, no published studies addressing blood brain barrier penetration were found so far but it has been postulated by Michel and his colleagues (2013) that although most ARBs exhibit little penetration into the brain, but may do so to great extent better when the blood brain barrier has become more permissive under pathologic conditions.

Evidence of improvements in cognition and mood following administration of some ACE inhibitors have clearly demonstrated that such effects are associated with an increase in dopamine and serotonin brain level (Jenkins, 2008) suggesting a primary role of both neurotransmitters. An extended role of these two neurotransmitters to anticonvulsive effect can be proposed. This suggestion should be strongly considered since a wide literature exist on anticonvulsant effects of several drugs mediated by one or both neurotransmitters (Chapman et al., 1984; De Sarro et al., 2002). More advanced neurochemical studies on this subject including a possible role of brain monoamines are required.

When interpreting the present results, interactions of the tested drugs with GABA ergic inhibitory neurotransmission should be also considered since GABA is the major inhibitory neurotransmitter in the brain, and it is responsible for the control of seizures (Czuczwar and Patsalos, 2001). Valproic acid is a drug which may act via increasing the content of GABA in nerve terminals (Loscher, 2002) and it seems reasonable to assume that potentiating the anticonvulsant effect of valproate may involve GABA-mimetic properties. The depressor effect of GABA in 2-kidney, 1-clip renovascular hypertensive rats was evaluated and shown to be mediated, at least in part, by inhibiting brain angiotensin system (Sun and Li, 1994).Accordingly, one accepted suggestion is that inhibiting brain RAAS may result in mediating the GABA inhibitory action in brains of mice suffering from seizures upon treatment with pilocarpine.

Another possible explanation, considering an indirect action of ACE inhibitors, might be related to the metabolic degradation of accumulated angiotensin I by other enzymes different from ACE such as tonin and cathepsin G (Stragier et al., 2008).One of the metabolites is angiotensin IV(AngIV)which has demonstrated an anticonvulsant activity against pilocarpine-induced seizures via dopamine and GABA release in the brain (Stragier et al., 2006). Other researches also highlighted a possible role for Ang IV in the regulation of brain functions in physiological and pathological conditions such as epilepsy and brain ischemia (Tchekalarova et al., 2001; Stragier et al., 2008).

The significant increase in the latency of convulsion observed in this study is an action similar to that of the standard anticovulsant drug diazepam. The latter postulated mechanism in this regard is believed to involve enhancement of GABA-ergic neurotransmission by increasing chloride ion flux through the chloride-ion channels at $GABA_A$-receptor sites (Olsen et al., 1981). Therefore, it is likely that the significant delay of seizures onset achieved by our tested drugs may involve opening of the chloride-ion channels associated with $GABA_A$-receptors, a mechanism which has to be proven by further studies.

In conclusion, this study revealed that lisinopril and valsartan enhanced the anticonvulsant action of VPA in mice with pilocarpine-induced seizures and that these interactions were pharmacodynamic in nature. The combinations of either drug with VPA decreased the brain insult caused by seizures and prolonged the latency to seizure appearance. Based on the current preclinical data, it is suggested that RAAS inhibition may positively interact with VPA in epileptic patients.

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