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Interactions between ACE inhibitors and classical antiepileptic drugs in the mouse maximal electroshock seizures

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ABSTRACT

This study evaluated the effect of two angiotensin-converting enzyme (ACE) inhibitors, enalapril and cilazapril, commonly used antihypertensive drugs, on the protective efficacy of the classical antiepileptics — carbamazepine (CBZ), phenytoin (PHT), valproate (VPA) and phenobarbital (PB). For this purpose, we used the maximal electroshock seizure (MES) test in mice. Additionally, adverse effects of combined treatment with ACE inhibitors and antiepileptic drugs in the passive avoidance task and chimney test were assessed. All drugs were administered intraperitoneally. Neither enalapril (10, 20 and 30 mg/kg) nor cilazapril (5, 10 and 20 mg/kg) affected the threshold for electroconvulsions. Enalapril (30 mg/kg) but not cilazapril (20 mg/kg), enhanced the protective action of VPA, decreasing its ED_{50} value from 249.5 to 164.9 mg/kg ($p<0.01$). Free plasma (non-protein-bound) and total brain concentrations of VPA were not significantly influenced by enalapril. Therefore, the observed interaction could be pharmacodynamic in nature. The combinations of ACE inhibitors with other antiepileptics (CBZ, PHT, and PB) were ineffective in that their ED_{50} values against MES were not significantly changed. Enalapril and cilazapril remained ineffective as regards memory retention in the passive avoidance task or motor performance in the chimney test. The current study suggests that there are no negative interactions between the studied ACE inhibitors and classical antiepileptic drugs. Enalapril was even documented to enhance the anticonvulsant activity of VPA.

1. Introduction

Angiotensin-converting enzyme (ACE) inhibitors affect renin-angiotensin system (RAS) in blood. ACE inhibitors block the conversion of angiotensin I (Ang I) to the active vasoconstrictor angiotensin II (Ang II), thereby lower blood pressure and improve cardiac function (Thind, 1990). ACE inhibitors also decrease aldosterone and vasopressin secretion and sympathetic nerve activity (Atlas, 2007). Furthermore, the existence of a brain RAS as one of various tissue RASs is established (Unger et al., 1988). Ang II exerts its actions through AT_1 and AT_2 receptors in different brain areas (de Gasparo et al., 2000). A number of these areas including the hippocampus, amygdala and piriform cortex, are involved in seizure susceptibility regulation (Jefferys, 1998; Löscher and Ebert, 1996; Myhrer, 2010). It has been suggested that the brain RAS can be an important target for inhibitors of the RAS such as ACE inhibitors and angiotensin AT_1 receptor antagonists since activation of brain AT_1 receptors increases blood pressure, fluid intake, natriuresis and vasopressin release (Gohlke et al., 2001). Additionally, the brain RAS seems to be implicated in stress, anxiety, depression, cognition, and epilepsy (De Bundel et al., 2008). It is noteworthy that intracerebroventricular Ang II may affect seizure susceptibility. Actually, it increases the seizure threshold for pentylenetetrazol (PTZ), bicuculline and picrotoxin, and attenuates the intensity of clonic convulsions evoked by PTZ in mice (Tchekalarova and Georgiev, 2005). Other angiotensin peptides, Ang III and Ang IV, have been shown to possess anticonvulsant properties too (Tchekalarova and Georgiev, 2005). On the other hand, some ACE inhibitors have been also documented to influence seizures in animals. Captopril, which contains an active sulfhydryl group, is the first oral and potent ACE inhibitor and it was followed by the introduction of nonsulfhydryl ACE inhibitors (Thind, 1990). This ACE inhibitor protected mice against seizures induced by strychnine and PTZ (Minano et al., 1987). Furthermore, captopril potentiated the anticonvulsant activity of carbamazepine and lamotrigine in the maximal electroshock seizure (MES) test in mice (Łukawski et al., 2010a), which is regarded as an experimental model of tonic-clonic seizures and, to a certain extent, of partial convulsions with or without secondary generalization (Löscher et al., 1991).

In this study, the effects of two nonsulfhydryl ACE inhibitors, enalapril and cilazapril, on the protective action of the classical antiepileptics — carbamazepine (CBZ), phenytoin (PHT), valproate (VPA) and phenobarbital (PB) in the MES test were examined. Based on clinical practice, CBZ and VPA are first-line drugs for generalized tonic–clonic seizures in adult patients (Duncan et al., 2006). PHT and

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PB can be considered for these types of seizures, although the effective and safe use of PHT depends on the ability to monitor its concentration in serum (Duncan et al., 2006; Lasoń et al., 2011). Enalapril is a prodrug that is hydrolyzed and converted in the liver to its bioactive form enalaprilat (Gomez et al., 1985). Similarly, cilazapril is converted to its active metabolite, cilazaprilat, by ester hydrolysis in the liver (Gross et al., 1993). Both ACE inhibitors are widely used for treatment of arterial hypertension and heart failure (Kelly and O'Malley, 1990; Williams et al., 1989). Therefore, it is likely that epileptic patients may receive them due to other medical causes such as cardiovascular diseases. It is noteworthy that cardiovascular disorders appear more frequently in people with epilepsy (Gaitatzis et al., 2004).

2. Materials and methods

2.1. Subjects

The experiments were carried out on adult male Swiss mice (20–26 g). They were housed in colony cages. The laboratory temperature was 22 ± 2 °C on a 12:12 h light/dark cycle. The animals had free access to food and tap water ad libitum. The experimental groups consisting of 8–16 animals were made up at random. Each mouse was used only once. The experimental protocols and procedures described in this paper were approved by the Local Ethics Committee for Animal Experiments at the University of Life Sciences in Lublin and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

2.2. Drugs

The following drugs were used in the experiments: enalapril (Enarenal, Polpharma S.A., Poland), cilazapril (Inhibace, Roche, Switzerland), carbamazepine (Amizepin, Polpharma S.A., Poland), valproate magnesium (Dipromal, ICN Polfa S.A., Poland), phenytoin (Phenytoinum, Polfa, Poland) and phenobarbital (Luminalum, Unia, Poland). VPA was dissolved in distilled water. Enalapril, cilazapril, CBZ, PHT and PB were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA) in distilled water. All drugs were injected intraperitoneally (i.p.) in a volume of 5 ml/kg body weight except for cilazapril which was administered in the volume of 10 ml/kg; control animals received injections of the vehicle. Cilazapril and PHT were administered 120 min, PB 60 min, enalapril 45 min, CBZ and VPA 30 min before the tests. The pretreatment times of the tested drugs were based upon the literature (Czuczwar et al., 1998; Minano et al., 1987; Waterfall, 1989).

2.3. Electroconvulsions

Electroconvulsions (50 Hz, 500 V, 0.2 s stimulus duration) were delivered *via* ear-clip electrodes produced by a Hugo Sachs generator (Rodent Shocker, Type 221, Freiburg, Germany). The endpoint was the tonic extension of the hind limbs. The convulsive threshold was evaluated as CS_{50}, which is the current strength (in mA) required to produce tonic hindlimb extension in 50% of the animals tested. To calculate the convulsive threshold, at least three groups of mice were challenged with electroshocks of various intensities. An intensity–response curve was calculated with a computer, based on a percentage of animals convulsing in experimental groups.

The protective activities of AEDs were determined as their ability to protect 50% of mice against the MES-induced tonic hindlimb extension and expressed as respective median effective doses (ED_{50} values in mg/kg). In the MES test, a fixed current intensity of 25 mA was applied. To evaluate the respective ED_{50} values, at least three groups of mice were challenged with the MES-induced seizures after receiving progressive doses of an AED. A dose–response curve for each AED was subsequently constructed on the basis of a percentage of animals protected against the seizures.

2.4. Step-through passive avoidance test

The pretreated mice with ACE inhibitors or in combinations with AEDs, were individually placed in an illuminated box (12 × 20 × 15 cm) connected to a dark box (24 × 20 × 15 cm). A 4 × 7 cm doorway was located at floor level in the center of the connecting wall. The dark box was equipped with an electric grid floor. Entrance into the dark box was punished by an electric foot shock (0.6 mA for 2 s). Twenty four hours after the training trial, the retention test was conducted in which the same animals with no treatment, were put into the illuminated box and the latency (time) to enter the dark box was recorded. The mice that avoided the dark compartment for 180 s were considered to remember the task. The passive avoidance test is generally regarded as a measure of long-term memory (Venault et al., 1986).

2.5. Chimney test

Motor performance was evaluated with the chimney test. The pretreated animals with ACE inhibitors or in combinations with AEDs, had to climb backwards up a plastic tube (3 cm inner diameter and 25 cm in length). Motor impairment was indicated as the inability of mice to climb backward up the tube within 60 s.

2.6. Estimation of plasma and brain concentrations of valproate

The measurement of the free plasma (non-protein-bound) and total brain concentrations of VPA was undertaken at a dose of the antiepileptic drug corresponding to its ED_{50} value in combination with enalapril (30 mg/kg) in the MES test. Mice were killed by decapitation at times scheduled for the MES test and blood samples of approximately 1 ml were collected into heparinized Eppendorf tubes. Simultaneously, the whole brains of mice were removed from skulls, weighed and homogenized using Abbott buffer (1:2 weight/volume) in an Ultra-Turrax T8 homogenizer (Staufen, Germany). The homogenates were centrifuged at 10,000 × *g* for 10 min. Blood samples were centrifuged at 5000 × *g* for 5 min, and plasma samples of 250 μl were transferred to a micropartitioning system, MPS-1 (Amicon, Danvers, MA, USA), for the separation of free from protein-bound microsolutes. Then, the MPS-1 tubes were centrifuged at 5000 × *g* for 10 min, and samples of 60 μl filtrate or 60 μl supernatant, appropriately diluted so as to fall within the linear concentration range, were analyzed for VPA content by fluorescence polarization immunoassay using a TDx analyzer and reagents exactly as described by the manufacturer (Abbott Laboratories, North Chicago, IL, USA). The free plasma and total brain concentrations of VPA were expressed in μg/ml of plasma or brain supernatant as the means ± S.D.

2.7. Statistics

Both CS_{50} and ED_{50} values were calculated by computer log-probit analysis according to Litchfield and Wilcoxon (1949). The 95% confidence limits obtained were transformed into standard errors of the mean (S.E.M.) as described previously (Łuszczki et al., 2003). The effects of ACE inhibitors on the convulsive threshold were analyzed with a one-way ANOVA followed by a post hoc Dunett's test for multiple comparisons. The anticonvulsant activities of AEDs injected alone or in combination with ACE inhibitors, were analyzed using the log-probit method for single comparisons and the one-way ANOVA followed by the post hoc Dunett's test. Results from the passive avoidance task were statistically compared using a Kruskal–Wallis non-parametric ANOVA followed by a Dunn's multiple comparisons test. Fisher's exact probability test was employed for the evaluation of data obtained in the chimney test. Free (non-protein-bound) plasma

and total brain concentrations of VPA were analyzed using unpaired Student's *t*-test. Group differences were considered statistically significant at $p<0.05$.

3. Results

3.1. Electroconvulsions

Both enalapril (10, 20 and 30 mg/kg i.p.) and cilazapril (5, 10 and 20 mg/kg i.p.) did not affect the threshold for electroconvulsions (results not shown). In the MES test, enalapril (30 mg/kg i.p.) potentiated the anticonvulsant action of VPA, reducing its ED_{50} value from 249.5 to 164.9 mg/kg ($p<0.01$). Combined treatments of enalapril with CBZ, PHT or PB resulted in no significant changes of the respective ED_{50} values of the classical antiepileptic drugs. Cilazapril did not influence the protective action of any of the tested antiepileptics (Table 1).

3.2. Passive avoidance and chimney test

As shown in Table 2, enalapril (30 mg/kg i.p.) and cilazapril (20 mg/kg i.p.) injected separately or co-administered with VPA, CBZ, PHT or PB at their ED_{50} values, did not impair memory retention in the passive avoidance task. Similarly, motor performance in the chimney test was not affected by ACE inhibitors injected alone or in combination with the studied antiepileptics (Table 3).

3.3. Effect of enalapril on plasma and total brain concentrations of valproate

Enalapril (30 mg/kg) did not significantly alter either free plasma or total brain concentrations of VPA (Table 4). Therefore, the observed interaction between enalapril and VPA could be pharmacodynamic in nature.

4. Discussion

It has been previously shown that losartan and telmisartan, two angiotensin AT_1 receptor antagonists, enhanced the protective action of VPA against MES-induced seizures in mice (Łukawski et al., 2010b). The major finding of this paper is that enalapril, a nonsulfhydryl ACE inhibitor, also increased the anticonvulsive activity of VPA, without contribution of pharmacokinetic factors.

At present, a role of brain RAS and mechanisms involved in this phenomenon remain unknown. Enalapril is capable of reducing ACE activity in the brain (Jouquey et al., 1995; Yamada et al., 2010). Cilazapril, another ACE inhibitor, which did not affect the protective activity of any of the studied antiepileptic drugs, is unable to cross the blood–brain barrier (Hirawa et al., 1999). The lack of a direct inhibition of the brain ACE, distinguishes cilazapril from enalapril, and may influence its action. On the other hand, high Ang I levels generated during peripheral ACE inhibition may interact with the brain ACE for local central conversion to Ang II and consequently cause central effects e.g. stimulate water or salt intake (Thunhorst et al., 1989). Ang II is also suggested to be implicated in the control of seizure susceptibility (Tchekalarova and Georgiev, 2005). However, the peripheral activity of ACE inhibitors and its influence on brain Ang II, do not seem to affect MES-induced convulsions since cilazapril was ineffective in this study. In the previous study, captopril, a potent inhibitor of the brain ACE (Evered et al., 1980), did not improve the protection of mice injected with VPA, however, it potentiated the anticonvulsant activity of CBZ and lamotrigine in the MES test (Łukawski et al., 2010a). Regardless, the combination of enalapril with lamotrigine has not been tested in this study, considering the different action of enalapril and captopril, the inhibition of brain ACE, per se, does not appear to be responsible for the anticonvulsant activity of enalapril. Divergent effects of enalapril and captopril have been reported in animal studies earlier. For example, in contrast to captopril, enalapril did not protect mice against strychnine-induced seizures, and even exacerbated them when administered intraperitoneally (Minano et al., 1987). Captopril potentiated morphine analgesia (Türker et al., 1979) whereas enalapril did not show this action

Table 1
Interactions between ACE inhibitors and classical antiepileptic drugs in the MES test.

Treatment (mg/kg)	ED_{50} (mg/kg)	N	S.E.M.
CBZ + vehicle	9.2 (8.0–10.7)	24	0.688
CBZ + enalapril (30)	11.3 (10.4–12.3)	16	0.845
CBZ + cilazapril (20)	9.6 (8.2–11.2)	16	0.913
PHT + vehicle	9.8 (7.9–12.1)	8	1.082
PHT + enalapril (30)	10.5 (9.1–12.1)	8	0.760
PHT + cilazapril (20)	10.8 (9.7–12.0)	8	0.807
VPA + vehicle	249.5 (227.5–273.7)	48	11.716
VPA + enalapril (30)	164.9 (133.3–204.0)**	24	20.693
VPA + enalapril (20)	255.0 (218.7–297.3)	16	19.909
VPA + cilazapril (20)	233.2 (182.3–298.3)	16	29.207
PB + vehicle	23.5 (20.2–27.3)	48	1.809
PB + enalapril (30)	20.1 (16.5–24.6)	24	2.068
PB + cilazapril (20)	18.7 (15.4–22.6)	16	1.840

Results are expressed as the median effective doses (ED_{50} in mg/kg) with 95% confidence limits (in parentheses) and S.E.M. values. CBZ — carbamazepine, PHT — phenytoin, VPA — valproate and PB — phenobarbital. N is the number of animals at those doses for which anticonvulsant effects ranged between 4 and 6 probit (16% and 84%) according to Litchfield and Wilcoxon (1949). **$p<0.01$ *vs.* VPA + vehicle (ANOVA/Dunnett's test).

Table 2
Effect of combined treatment with ACE inhibitors and antiepileptics on retention in the passive avoidance test.

Treatment (mg/kg)	N	Latency (s)
Control	8	180 (176, 180)
Enalapril (30)	8	180 (151, 180)
CBZ (11.3) + enalapril (30)	8	180 (180, 180)
PB (20.1) + enalapril (30)	8	180 (160, 180)
PHT (10.5) + enalapril (30)	8	180 (114, 180)
VPA (164.9) + enalapril (30)	8	180 (146, 180)
Control	8	180 (159, 180)
Cilazapril (20)	8	180 (137, 180)
CBZ (9.6) + cilazapril (20)	8	180 (180, 180)
PB (18.7) + cilazapril (20)	8	180 (180, 180)
PHT (10.8) + cilazapril (20)	8	175 (75, 180)
VPA (233.2) + cilazapril (20)	8	180 (165, 180)

Results are presented as median values (in s) along with 25th and 75th percentiles. CBZ — carbamazepine, PHT — phenytoin, VPA — valproate and PB — phenobarbital. N is the number of animals. Not significant *vs.* control groups (Kruskal–Wallis non-parametric ANOVA/Dunn's test).

Table 3
Effect of combined treatment with ACE inhibitors and antiepileptics on motor performance in the chimney test.

Treatment (mg/kg)	N	Percentage of mice impaired (%)
Control	8	0
Enalapril (30)	8	0
CBZ (11.3) + enalapril (30)	8	0
PB (20.1) + enalapril (30)	8	12.5
PHT (10.5) + enalapril (30)	8	0
VPA (164.9) + enalapril (30)	8	0
Control	8	0
Cilazapril (20)	8	12.5
CBZ (9.6) + cilazapril (20)	8	0
PB (18.7) + cilazapril (20)	8	0
PHT (10.8) + cilazapril (20)	8	12.5
VPA (233.2) + cilazapril (20)	8	0

Data are expressed as percentage of animals that failed to perform in the chimney test. CBZ — carbamazepine, PHT — phenytoin, VPA — valproate and PB — phenobarbital. N is the number of animals. Not significant *vs.* control groups (Fisher's exact probability test).

Table 4
Influence of enalapril on plasma and total brain concentrations of valproate.

Treatment (mg/kg)	Plasma concentrations (μg/ml)	Brain concentrations (μg/ml)
VPA (164.9) + vehicle	218.228 ± 71.972	17.522 ± 6.616
VPA (164.9) + enalapril (30)	229.676 ± 79.032	19.972 ± 5.890

Data are presented as the means ± S.D. of eight separate determinations. Not significant *vs.* control group (Student's *t*-test).

(Mojaverian et al., 1984). It has been suggested that these effects of captopril, can be, at least in part, related to a presence of the sulfhydryl group of the compound (Minano et al., 1987; Mojaverian et al., 1984). Also, captopril-induced enhancement of the anticonvulsant activity of CBZ seems to be the unique feature of captopril, likely related to its chemical properties and/or an influence of captopril on the glycinergic system (Łukawski et al., 2010a). In this study, enalapril, a nonsulfhydryl drug, potentiated the antiseizure action of VPA but not CBZ, which is in agreement with the study on AT_1 receptor antagonists, losartan and telmisartan, in the MES test (Łukawski et al., 2010b). It is noteworthy that both enalapril and these two AT_1 receptor antagonists have been documented to protect against glutamate-mediated neurotoxicity (Ravati et al., 1999; Wu et al., 2010). Therefore, the improved protection of mice co-administered with enalapril and VPA against MES-induced seizures may be related to the glutamatergic system. It is well known that excitatory amino acids including glutamate are involved in the generation of seizure events (Meldrum, 1984). One of multiple mechanisms of antiepileptic activity of VPA seems to be the antagonism of *N*-methyl-D-aspartate (NMDA) receptor-mediated neuronal excitation (Löscher, 2002). Competitive and non-competitive NMDA receptor antagonists applied in combination with VPA augment its anticonvulsant activity in the MES test (Czechowska et al., 1993; Urbańska et al., 1991). It is noteworthy that among tested antiepileptics in the current study, only VPA was able to block seizures evoked by systemic administration of NMDA in mice (Czuczwar et al., 1985). Also VPA, but not CBZ, PHT and PB, was effective against intracerebroventricular NMDA in mice (Turski et al., 1990). On the other hand, enalapril attenuated a pressor response to microinjection of NMDA in rostral ventrolateral medulla in spontaneous hypertensive rats (Tsuchihashi et al., 1998). It has been suggested that enalapril itself may have an influence on rostral ventrolateral medulla neurons to reduce their responsiveness to excitatory amino acids, although the prevention of hypertension by enalapril is more likely as a dominant mechanism in this case (Tsuchihashi et al., 1998). Additionally, it has been demonstrated that enalapril was protective against glutamate-induced damage in cultured neurons and it reduced ischemic brain injury in mice in vivo probably due to its ability to scavenge reactive oxygen species (Ravati et al., 1999). Thus, we cannot exclude that the combined treatment with enalapril and VPA could provide better protection against neuronal excitation induced by glutamate and therefore convulsions. However, it would be of interest to perform neurochemical studies on this issue.

In conclusion, the present study showed that enalapril enhanced the anticonvulsant activity of VPA and this combined treatment was free from side-effects on motor performance and long-term memory in mice. This interaction was not pharmacokinetic in nature as enalapril did not change the brain and plasma level of VPA. From the preclinical point of view, there are no negative interactions between the studied ACE inhibitors and classical antiepileptic drugs. Enalapril may positively interact with VPA in epileptic patients.

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