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Short communication

Enalapril enhances the anticonvulsant activity of lamotrigine in the test of maximal electroshock

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Abstract:
Background: The aim of this study was to find out whether angiotensin-converting enzyme (ACE) inhibitors, enalapril and cilazapril, affect the anticonvulsant action of some second-generation antiepileptics, lamotrigine (LTG), topiramate (TPM) and oxcarbazepine (OXC).
Methods: The effects of ACE inhibitors on antiepileptic drugs were examined in the mouse model of maximal electroshock.
Results: Enalapril (30 mg/kg *ip*) potentiated the anticonvulsant action of LTG, decreasing its ED_{50} value from 5.3 to 3.6 mg/kg ($p < 0.01$). The anticonvulsant activity of TPM or OXC was not modified by enalapril. Cilazapril did not affect the protective activity of the studied antiepileptics. The interaction between enalapril and LTG could be pharmacodynamic in nature because enalapril did not change plasma and total brain concentrations of LTG.
Conclusions: This study shows that there are no negative interactions between the studied antiepileptic drugs and enalapril or cilazapril. Enalapril even enhanced the anticonvulsant activity of LTG in the MES test in mice that is thought to be a predictive model of human generalized tonic-clonic seizures.

Key words:
ACE inhibitors, antiepileptic drugs, maximal electroshock, seizure

Introduction

Inhibition of angiotensin-converting enzyme (ACE) which catalyzes the formation of angiotensin II, a potent vasoconstrictor, from circulating angiotensin I, significantly lowers systemic vascular resistance, lowers blood pressure, and improves cardiac function [25]. Hence, ACE inhibitors are widely used for the treatment of arterial hypertension and heart failure [25]. Besides the peripheral, all components of the renin-angiotensin system (RAS) are localized in the brain [26]. The brain RAS seems to be implicated in stress, anxiety, depression, cognition and epilepsy [5]. Animal studies have shown that certain ACE inhibitors may possess an anticonvulsant-like activity. Recently, it has been reported that enalapril, a nonsulfhydryl ACE inhibitor [25], impaired the triggering and maintenance of seizures in the rat audiogenic model of epilepsy [20]. Enalapril also enhanced the protective action of valproate in the mouse model of maximal electroshock (MES), although it did not affect the anticonvulsant action of other classical antiepileptic drugs (AEDs), i.e., carbamazepine, phenytoin and

phenobarbital [13]. In this study, we examined the effects of enalapril and additionally cilazapril, another ACE inhibitor and a commonly prescribed antihypertensive agent [23], on the anticonvulsant activity of some second-generation AEDs, lamotrigine (LTG), oxcarbazepine (OXC) and topiramate (TPM) in the MES model. Enalapril and cilazapril are prodrugs that are converted to their active metabolites, enalaprilat and cilazaprilat, in the liver [8]. LTG is an antiepileptic drug which has a broad spectrum of activity, with efficacy against partial, absence, myoclonic and tonic-clonic seizures [9]. The main indication for OXC is in the treatment of partial seizures [10]. TPM can be used against many types of epileptic seizures, including drug-resistant convulsions [10]. Additionally, LTG and TPM belong to AEDs that are mostly recommended to epileptic patients suffering from cardiovascular diseases [22].

Materials and Methods

Animals and drugs

The study was conducted on male Swiss mice (20–26 g). Animals were kept under standardized laboratory conditions (a 12-h light-dark cycle, temperature of 21 ± 1°C) in colony cages with free access to food and tap water *ad libitum*. The experimental groups consisting of 8–16 animals were made up at random. The experimental protocols and procedures described in this paper were approved by the Local Ethics Committee for Animal Experiments and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Enalapril (Enarenal, Polpharma S.A., Poland), cilazapril (Inhibace, Roche, Switzerland), OXC (Trileptal, Novartis Pharma GmbH, Germany), LTG (Lamitrin, GlaxoSmithKline, UK) and TPM (Topamax, Janssen-Cilag International N.V., Belgium) were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA) in distilled water. The drugs were administered intraperitoneally (*ip*) in a volume of 5 ml/kg body weight except for cilazapril which was injected in the volume of 10 ml/kg. Cilazapril was administered 120 min, LTG and TPM 60 min, enalapril 45 min and OXC 30 min before the tests. The pretreatment times were taken from previous reports [13, 14, 18]. The dose range of 20–30 mg/kg for enalapril used in this study was based on previous experiments showing some central effects of enalapril [4, 13, 19]. A dose of cilazapril (20 mg/kg) was the highest dose used in the earlier study on interactions with classical AEDs [13] and it was applied here for comparison.

MES test

Electroconvulsions (25 mA, 50 Hz, 500 V, 0.2 s stimulus duration) were produced by a Hugo Sachs generator (Rodent Shocker Type 221, Freiburg, Germany) and delivered *via* standard auricular electrodes. The endpoint was the tonic extension of the hind limbs. 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). To evaluate the respective ED_{50} values for AEDs alone and in combinations with ACE inhibitors, at least three groups of mice were challenged with MES after receiving different doses of an AED in order to obtain a variable percentage of protection against MES. On this basis, a dose-response curve for each AED was subsequently constructed according to Litchfield and Wilcoxon [11]. To determine the ED_{50} values for AEDs, LTG was administered at doses ranging between 3 and 7 mg/kg, OXC at doses ranging between 8 and 18 mg/kg and TPM at doses ranging between 20 and 90 mg/kg.

Passive avoidance and chimney test

Possible adverse effects of combined treatment with ACE inhibitors and AEDs, such as an impairment of memory retention in the passive avoidance task [27] or disturbed motor coordination in the chimney test [1], were also evaluated. In the passive avoidance task, the pretreated mice were individually placed in an illuminated box (12 × 20 × 15 cm) connected to a dark box (24 × 20 × 15 cm) and were punished by an electric foot shock (0.6 mA for 2 s) when entering the dark box. Twenty four hours later, the retention test was conducted in which the same animals with no further pretreatment, 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. In the chimney test, the pretreated animals had to climb backwards up a plastic tube (3 cm inner diameter and 25 cm in length). Motor impairment was indi-

cated as the inability of mice to climb backward up the tube within 60 s. In both tests, mice co-administered with ACE inhibitors and AEDs at doses corresponding to their ED_{50} values, were compared to control mice injected with vehicle. The design of these experiments was based on previous reports [16] and data showing that ACE inhibitors and AEDs alone at doses applied in this study did not affect retention in the passive avoidance task or motor coordination in the chimney test [2, 3, 17].

Measurement of LTG concentrations

Plasma and brain levels of LTG were estimated by high-performance liquid chromatography (HPLC). Mice were decapitated at times chosen to coincide with that scheduled for the MES test and blood samples of approximately 1 ml were collected into heparinized Eppendorf tubes. Simultaneously, the brains of mice were removed from their skulls and placed into the deep freeze at –80°C. Samples of blood were centrifuged at 5,000 × g for 5 min, and plasma samples of 200 µl were stocked into the deep freeze. On the next day, plasma samples and the brains were removed from the freeze. The brains were weighed and homogenized using Abbott buffer (1 : 2 w/v) in an Ultra-Turrax T8 homogenizer (IKA, Staufen, Germany). The homogenates were centrifuged at 10,000 × g for 10 min. Plasma and brain supernatant samples were prepared for analysis as follows: 200 µl of samples were pipetted into a 1.5 ml plastic tube to which was added 200 µl of 0.08 M triethylammonium phosphate buffer solution, 400 µl of acetonitrile, and vortex-mixed for 1 min. After centrifugation (10,000 × g for 10 min) in centrifugal filter devices (Millipore Corporation), the organic layer was removed and 20 µl of the aqueous phase was injected into HPLC system. The chromatograph (Dionex, Sunnyvale, CA, USA) was equipped with a gradient pump P580 LPG and a UV/VIS detector (UVD 340S) with a sensitivity setting of 0.1 absorbance units full scale (AUFS) and a time constant of 0.1 s. The Rheodyne 3601 injector valve with a 20 µl sample loop was used for sample injection. For HPLC, a stainless steel HP ODS column (200 × 4.6 mm) was used at an ambient temperature. The mobile phase was 40 mM triethylammonium phosphate buffer: methanol : acetonitrile (660 : 80 : 160 v/v/v; Fluka, HPLC grade). The mobile phase flow rate was 1.2 ml/min, and LTG absorbance was measured at 214 nm. The peak height for LTG was linearly related to its concentrations, which ranged from 0.16 to 5.0 g/ml. Plasma levels or total brain concentrations of LTG were expressed in µg/ml of plasma or supernatant as the means ± SD of eight determinations.

Data analysis

ED_{50} values were calculated by computer log-probit analysis [11] and the 95% confidence limits obtained were transformed to standard errors of the mean (SE) as described previously [15]. The anticonvulsant activities of AEDs injected alone or in combination with ACE inhibitors, were compared with the use of one-way ANOVA followed by the *post-hoc* Dunnett's test. A Kruskal-Wallis non-parametric ANOVA and Dunn's multiple comparisons test were used to analyze results from the passive avoidance task. Data obtained in the chimney test were statistically evaluated by Fisher's exact probability test. The plasma and total brain concentrations of LTG were analyzed using unpaired Student's *t*-test. Group differences were considered statistically significant at $p < 0.05$.

Results

In the MES test, enalapril (30 mg/kg *ip*) potentiated the anticonvulsant activity of LTG, decreasing its ED_{50} value from 5.3 to 3.6 mg/kg ($p < 0.01$, Dunnett's test). Enalapril did not affect the protective action of OXC and TPM. Combined treatments of cilazapril (20 mg/kg *ip*) with AEDs, did not result in any significant changes in the ED_{50} values against MES (Tab. 1). The interaction between enalapril and LTG could be pharmacodynamic in nature as enalapril did not change plasma or total brain concentrations of LTG (Tab. 2). None adverse effects were observed in the passive avoidance task (Fig. 1) and the chimney test (Tab. 3) after simultaneous administration of studied ACE inhibitors and AEDs.

Discussion

Previous study has shown that enalapril up to the dose of 30 mg/kg *ip* and cilazapril up to the dose of

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

Treatment (mg/kg)	ED_{50} (mg/kg)	n	SE
LTG + vehicle	5.3 (4.9 – 5.7)	40	0.224
LTG + enalapril (30)	3.6 (2.6 – 5.0) **	16	0.600
LTG + enalapril (20)	5.0 (4.2 – 6.0)	16	0.463
LTG + cilazapril (20)	5.0 (4.2 – 5.8)	24	0.411
	F (3, 92) = 3.343, p = 0.0226		
OXC + vehicle	14.4 (12.4 – 16.7)	16	1.335
OXC + enalapril (30)	12.0 (9.7 – 14.8)	24	1.482
OXC + cilazapril (20)	13.1 (11.6 – 14.8)	48	0.879
	F (2, 85) = 0.6996, p = 0.4996		
TPM + vehicle	46.1 (38.0 – 55.8)	48	4.503
TPM + enalapril (30)	59.5 (43.1 – 82.2)	40	9.792
TPM + cilazapril (20)	31.5 (20.9 – 47.6)	24	7.655
	F (2, 109) = 2.870, p = 0.0610		

Results are expressed as the median effective doses (ED_{50} in mg/kg) with 95% confidence limits (in parentheses) and SE values. n – The number of animals at those doses for which anticonvulsant effects ranged between 4 and 6 probit, according to Litchfield and Wilcoxon [11]. The number of comparisons between control and examined groups with Dunnett's test was two or three, depending on the experiment. Dunnett's test is regarded as a conservative one in controlling type 1 error. ** $p < 0.01$ *vs.* LTG + vehicle (ANOVA/Dunnett's test)

Tab. 2. Effect of enalapril on plasma and total brain concentrations of LTG

Treatment (mg/kg)	Plasma concentrations (μg/ml)	Brain concentrations (μg/ml)
LTG (3.6) + vehicle	1.709 ± 0.129	0.692 ± 0.189
LTG (3.6) + enalapril (30)	1.593 ± 0.200	0.709 ± 0.142

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

Tab. 3. Interactions between ACE inhibitors and antiepileptic drugs in the chimney test

Treatment (mg/kg)	n	% of mice impaired
Control	8	0
LTG (3.6) + enalapril (30)	8	0
OXC (12) + enalapril (30)	8	12.5
TPM (59.5)+ enalapril (30)	8	12.5
Control	8	0
LTG (5.0) + cilazapril (20)	8	0
OXC (13.1) + cilazapril (20)	8	0
TPM (31.5)+ cilazapril (20)	8	0

Results are presented as the percentage of animals that failed to perform the chimney test. Control animals received injections of the vehicle. n – The number of animals. Not significant *vs.* control groups (Fisher's exact probability test)

20 mg/kg *ip*, did not affect the convulsive threshold [13]. In this study, we used the same subthreshold doses for these ACE inhibitors. Enalapril has been found to enhance the anticonvulsant activity of LTG in the MES test, without affecting the brain and plasma concentrations of LTG.

The present finding is in agreement with a recent study on the interactions between ACE inhibitors and AEDs in the audiogenic seizure model in DBA/2 mice [6]. De Sarro et al. have demonstrated that enalapril (30 mg/kg *ip*) was able to produce a significant reduction of ED_{50} value of LTG against clonus [6]. The exact mechanism of this finding remains unknown. It has been documented that acute administration of enalapril can affect behavior related to the central nervous system. For example, enalapril administered at the single dose of 20 mg/kg *ip* decreased ethanol-induced hyperactivity and reduced ethanol sleeping time in mice [4]. It has been suggested that enalapril interacts with ethanol in the brain, possibly due to its influence on neurotransmitter systems [4]. Also, enalapril given orally up to the single dose of 30 mg/kg, reduced the amnesiogenic effect of cerebral electroshock treatment and improved passive avoidance learning if administered before the learning trial in mice [19].

Recently, Pereira at al. reported that chronic oral treatment with enalapril (10 mg/kg) decreased seizure severity and significantly impaired activity of ACE in the hippocampus in Wistar audiogenic rats [20]. Further, enalaprilat, the active metabolite of enalapril, has been demonstrated to distribute in the brain when measured one hour after acute treatment [29]. This could suggest a possible role of the inhibition of the brain ACE by enalaprilat in the observed phenomenon. Moreover, cilazapril which is unable to cross the blood-brain barrier [7] did not show any anticonvul-

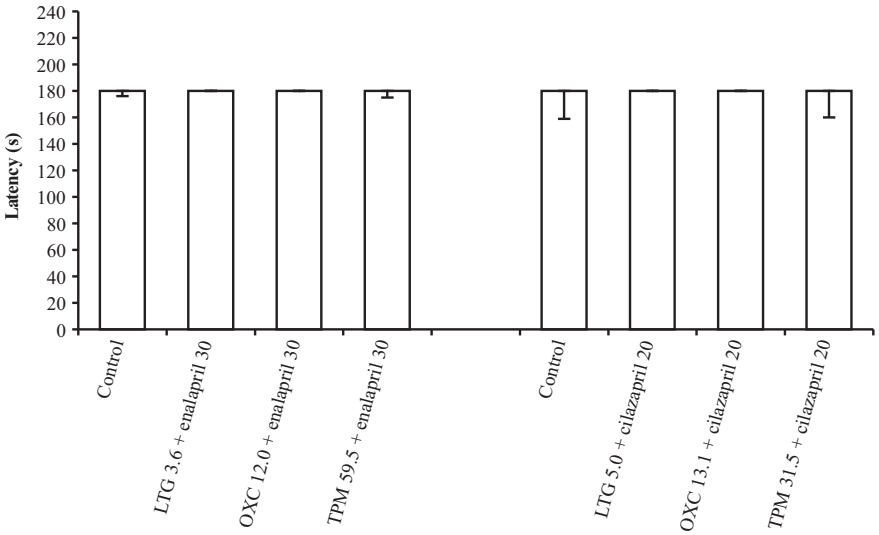

Fig. 1. Interactions between ACE inhibitors and antiepileptic drugs in the passive avoidance test. Data are shown as median values (in s) along with the 25th and 75th percentiles. Control animals received injections of the vehicle. Eight mice were examined in each group. Not significant *vs.* control groups (Kruskal-Wallis non-parametric ANOVA/Dunn's test)

sant activity indicating that the peripheral ACE inhibition has not been involved. On the other hand, a single oral administration of some ACE inhibitors including enalapril, has not been shown to affect the brain ACE [24]. Additionally, the lack of a positive effect between enalapril and TPM or OXC was observed in this study. Thus, the functional inhibition of the brain RAS, by the decreased activity of ACE, does not seem to be responsible for the phenomenon.

It is known that LTG inhibits voltage-dependent sodium and calcium currents, reduces veratridine-induced synaptic release of glutamate and is an effective antagonist of AMPA receptors [9, 10]. On the other hand, pharmacological mechanisms of AEDs, which are related to sodium channels, NMDA receptors, AMPA receptors and/or voltage-dependent calcium channels could be positively affected by certain ACE inhibitors in terms of seizure susceptibility [6]. It has been documented that enalapril was protective against glutamate-induced damage in cultured neurons [21]. It can be speculated that LTG combined with enalapril may provide enhanced protection against glutamate-induced neuronal excitation. This could lead to the positive effect observed in the MES test. The anticonvulsant action of OXC does not rather depend on the inhibition of glutamate excitation [10]. TPM inhibits glutamatergic system activity [10] but enalapril showed a tendency (statistically not significant) to diminish the anticonvulsant action of TPM rather than to enhance it. However, other mechanisms responsible for the better protection of mice injected with both LTG and enalapril against MES-induced seizures are also possible.

Enalapril and cilazapril have been used at doses at which their hypotensive activities should be assumed [28]. However, it seems very unlikely that this could interfere with the observed results in the MES test. None of the tested combinations of the drugs, including LTG (3.6 mg/kg) + enalapril (30 mg/kg) group, showed impaired motor coordination in the chimney test. Additionally, the combined treatment with LTG (3.5 mg/kg) and enalapril (30 mg/kg) did not influence the locomotor activity of mice in the rotarod test [6].

In conclusion, the combined treatment with the studied ACE inhibitors and OXC or TPM, and the combination of cilazapril with LTG seem neutral regarding the anticonvulsant potency of the antiepileptic drugs. Enalapril potentiated the anticonvulsant action of LTG in the MES test in mice that is thought to be a predictive model of human generalized tonic-clonic seizures [12].

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