Neurol Sci (2015) 36:779–781
DOI 10.1007/s10072-014-2040-x

BRIEF COMMUNICATION

Effect of ACE inhibitors and AT_1 receptor antagonists on pentylenetetrazole-induced convulsions in mice

Krzysztof Łukawski · Stanisław Jerzy Czuczwar

Received: 9 April 2014 / Accepted: 5 December 2014 / Published online: 9 January 2015

Abstract Experimental data show that some angiotensin-converting enzyme (ACE) inhibitors and angiotensin AT_1 receptor antagonists that are normally used as antihypertensive drugs can exert anticonvulsant-like activity against audiogenic seizures. In the current study, a number of ACE inhibitors (captopril, enalapril, cilazapril, perindopril and zofenopril) and AT_1 antagonists (losartan, telmisartan and candesartan) were examined against pentylenetetrazole (PTZ)-induced seizures in mice. Captopril (50 mg/kg) administered intraperitoneally significantly raised the PTZ threshold ($p < 0.05$). The remaining drugs were not protective against PTZ-induced convulsions. The current study indicates that captopril decreases PTZ-evoked seizures in mice, which is an animal model of myoclonic convulsions.

Keywords ACE inhibitor · AT_1 antagonist · Pentylenetetrazole · Seizure

The angiotensin-converting enzyme (ACE) inhibitors and angiotensin AT_1 receptor antagonists are widely prescribed drugs for hypertension and heart failure. There are experimental data showing that some ACE inhibitors and AT_1 antagonists may possess anticonvulsant-like activity. For example, fosinopril, zofenopril and captopril were able to decrease the severity of audiogenic seizures in mice [1]. Enalapril and losartan impaired the triggering and maintenance of seizures in the rat audiogenic model of epilepsy [2]. In this study, we sought to evaluate activities of ACE inhibitors and AT_1 antagonists against pentylenetetrazole (PTZ)-induced seizures in mice, generally recognized as an animal model of myoclonic convulsions.

Male Swiss mice (20–26 g) were used. Animals were housed under standardized laboratory conditions. The experimental procedures were approved by the Local Ethics Committee for Animal Experiments (license no. 65/2012).

ACE inhibitors: captopril (Jelfa), enalapril (Polpharma), cilazapril (Roche), perindopril (Servier), zofenopril (Berlin-Chemie), and AT_1 antagonists: losartan (Adamed), telmisartan (Boehringer Ingelheim) and candesartan (AstraZeneca), were suspended in a 1 % solution of Tween 80 (Sigma) and administered intraperitoneally (i.p.) in a volume of 0.005 or 0.01 ml/g (cilazapril). PTZ (Sigma) was injected subcutaneously. Treatment times were: 45 min (captopril, enalapril), 60 min (perindopril, zofenopril) and 120 min (cilazapril, losartan, telmisartan, candesartan). At least 4 groups of animals (8 mice per group) were administered with different doses of PTZ alone or in combinations with antihypertensive drugs. Following the injection of PTZ, animals were placed separately in transparent Plexiglass cages (25 × 15 × 10 cm) and observed for 30 min for the occurrence of clonic seizures. The clonic seizure activity was defined as clonus of the whole body lasting for over 3 s, with an accompanying loss of the righting reflex. CD_{50} value (median convulsive dose of PTZ inducing the seizure response in 50 % of mice) with their 95 % confidence limits were calculated by computer-assisted log-probit analysis [3]. Statistical analysis of data was performed by one-way ANOVA and the post hoc Dunnett's test.

Among tested ACE inhibitors (Table 1) and AT_1 antagonists (Table 2), only captopril (50 mg/kg i.p.)

K. Łukawski (✉) · S. J. Czuczwar
Department of Physiopathology, Institute of Rural Health, Jaczewskiego 2, Lublin 20-090, Poland
e-mail: lukaw@mp.pl

S. J. Czuczwar
Department of Pathophysiology, Medical University of Lublin, Jaczewskiego 8, Lublin 20-090, Poland

Table 1 Effect of ACE inhibitors on the threshold for pentylenetetrazole (PTZ)-induced seizures in mice

Treatment (mg/kg)	CD_{50} of PTZ	SEM	*n*
PTZ + vehicle	58.2 (52.4–64.6)	3.104	16
PTZ + captopril (50)	78.1 (69.1–88.3)*	5.630	24
PTZ + captopril (25)	66.5 (60.5–73.1)	3.221	16
PTZ + perindopril (10)	61.9 (53.5–71.5)	4.573	24
	$F_{3,76} = 3.611$; $p = 0.0170$		
PTZ + vehicle	63.2 (55.3–72.2)	4.963	24
PTZ + enalapril (30)	67.7 (57.4–80.0)	5.737	32
PTZ + cilazapril (20)	59.3 (52.3–67.2)	4.623	16
PTZ + zofenopril (30)	71.0 (56.7–89.0)	8.177	32
	$F_{3,100} = 0.5051$; $p = 0.6797$		

Results are shown as median convulsive doses (CD_{50} in mg/kg) of PTZ with 95 % confidence limits (in brackets) and SEM values

n the number of animals at doses of PTZ, for which convulsant effects were between 4 and 6 probits

* $p < 0.05$ vs PTZ + vehicle (Dunnett's test)

Table 2 Effect of AT_1 receptor antagonists on the threshold for pentylenetetrazole (PTZ)-induced seizures in mice

Treatment (mg/kg)	CD_{50} of PTZ	SEM	*n*
PTZ + vehicle	64.9 (57.4–73.4)	4.986	16
PTZ + losartan (50)	63.8 (56.0–72.8)	4.258	16
PTZ + telmisartan (30)	65.9 (59.8–72.7)	3.273	16
PTZ + candesartan (16)	59.3 (51.1–69.0)	4.539	16
	$F_{3,60} = 0.4565$; $p = 0.7137$		

Data are presented as median convulsive doses (CD_{50} in mg/kg) of PTZ with 95 % confidence limits (in brackets) and SEM values. $p > 0.05$ vs PTZ + vehicle (Dunnett's test)

n the number of animals at doses of PTZ, for which convulsant effects were between 4 and 6 probits

showed the protective effect against convulsions induced by PTZ ($p < 0.05$; Dunnett's test), which seems to rather exclude the inhibition of the brain renin-angiotensin system as the one responsible for the phenomenon. In our previous study, captopril (50 mg/kg i.p.) was ineffective against maximal electroshock (MES) [4]. De Sarro et al. [1] reported that captopril at doses higher than 80 mg/kg i.p. produced significant protection against the tonic phase of the audiogenic seizure response. Probably, Minano et al. [5] were the first to demonstrate the anticonvulsant-like activity of captopril in mice, showing that captopril (100–200 mg/kg i.p.) produced anticonvulsant effect against strychnine-induced seizures. They also reported that captopril protected mice against convulsions induced by PTZ [5], which is in agreement with the current study. When interpreting the effect of captopril against seizures induced by the $GABA_A$ receptor antagonist PTZ, an involvement of GABAergic system should be considered. Captopril might behave as a prodrug that could give rise to GABA-like metabolic products through pyrroline biotransformation [5]. However, captopril was ineffective against seizures induced by bicuculline, a competitive antagonist of $GABA_A$ receptors [5]. In the MES test, it did not potentiate the anticonvulsant action of phenobarbital that suppresses seizures by potentiating the effects of GABA [4]. It has been also suggested that the presence of a sulfhydryl group may be responsible for anticonvulsant-like activity of captopril [5]. However, zofenopril, another ACE inhibitor with the sulfhydryl group, did not show an anticonvulsant action in this study. Noteworthy, zofenopril was more active than captopril in decreasing the severity of audiogenic seizures in mice [1]. The anticonvulsant activity of captopril against PTZ may be related to an action on glycine receptors which are thought to play some role in the convulsant effects of PTZ [6]. It has been reported that PTZ may block glycine-induced currents via glycine receptors [6]. As already mentioned above, captopril antagonized convulsions induced by strychnine, a glycine receptor antagonist [5]. However, more advanced neurochemical studies are required to elucidate the exact molecular mechanism(s) responsible for the observed anticonvulsant effect of captopril.

It is evidently premature to suggest captopril as a drug of choice for the treatment of hypertension in patients with myoclonic seizures. However, data are available that captopril was used as an adjuvant for the management of catamenial epilepsy [7]. There is also evidence that the drug may potentiate the anticonvulsant activity of some antiepileptic drugs against audiogenic seizures and electroconvulsions in mice [1, 4]. If a positive interaction between captopril and some antiepileptic drugs against PTZ is confirmed then captopril might be also considered as an adjuvant in hypertensive patients with myoclonic seizures. A clinical study on the potential benefits of using captopril in such patients would be certainly necessary.

Acknowledgments This study was supported by a grant from Institute of Rural Health in Lublin.

Conflict of interest The authors have no conflict of interest.

References

1. De Sarro G, Paola ED, Gratteri S, Gareri P et al (2012) Fosinopril and zofenopril, two angiotensin-converting enzyme (ACE) inhibitors, potentiate the anticonvulsant activity of antiepileptic drugs against audiogenic seizures in DBA/2 mice. Pharmacol Res 65:285–296
2. Pereira MG, Becari C, Oliveira JA, Salgado MC et al (2010) Inhibition of the renin-angiotensin system prevents seizures in a rat model of epilepsy. Clin Sci (Lond) 119:477–482

3. Litchfield JT, Wilcoxon F (1949) A simplified method of evaluating dose-effect experiments. J Pharmacol Exp Ther 96:99–113
4. Łukawski K, Jakubus T, Raszewski G, Czuczwar SJ (2010) Captopril potentiates the anticonvulsant activity of carbamazepine and lamotrigine in the mouse maximal electroshock seizure model. J Neural Transm 117:1161–1166
5. Minano FJ, Serrano JS, Sancibrian M, Serrano MI (1987) Effect of peptidyl-dipeptidase inhibitors in experimental convulsions in mice. Fundam Clin Pharmacol 1:77–83
6. Jung ME, Lal H, Gatch MB (2002) The discriminative stimulus effects of pentylenetetrazol as a model of anxiety: recent developments. Neurosci Biobehav Rev 26:429–439
7. Millar JA, Neill KG (1991) Captopril as adjunctive treatment in catamenial epilepsy. N Z Med J 104:368–369