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Role of Cysteine Proteases in the Mechanism of Action of the Anticonvulsants Levetiracetam and Carbamazepine and the Calpain Inhibitor Calpastatin in Pentylenetetrazole-kindled Rats

[1]Mahmoud A. Mansour, [1]Awatif B. Albaker, [2]Ammar C. Al-Rikabi and [3]Abdulqader Alhaider
[1]Department of Pharmacology, Faculty of Pharmacy,
[2]Department of Pathology,
[3]Faculty of Medicine, King Saud University, P.O Box 2925, Riyadh 11461, Saudi Arabia

Abstract: Atypical antiepileptic drugs such as Levetiracetam (LEV) show antiepileptic activity in animals and humans; however their actions do not seem to be similar to the traditional antiepileptic drugs. The present study investigated the possible role of cysteine proteases in the mechanism of action of levetiracetam and the traditional antiepileptic Carbamazepine (CBZ) and calpain inhibitor; Calpastatin (CS) in kindled rats. The effect of increasing doses of CBZ (50, 100 and 200 mg kg^{-1}, p.o), LEV (13, 27 and 54 mg kg^{-1}, p.o.) and the calpain inhibitor, CS (1.59, 3.18 and 6.36 mg kg^{-1}, i.p.) on calpain, caspase 3 and cathepsin B were studied in normal and in kindled rats. Seizures induced by pentylenetetrazole increased the activity level of calpain, caspase 3 and cathepsin B (8.44±1.4 vs. 40.42±0.47 μmol min^{-1} mg^{-1} protein, $p<0.05$), (87.50±0.36 vs. 495.91±3.51 μmol min^{-1} mg^{-1} protein, $p<0.05$) and (88.89±0.38 vs. 500.66±2.51 μmol min^{-1} mg^{-1} protein, $p<0.05$), respectively in brain tissues homogenates. Treatment of fully kindled rats with different doses of CBZ and LEV caused a significant inhibition ($p<0.05$) of cysteine proteases activity in a significant dose dependent manner in rats brain homogenates. Moreover, the calpain inhibitor; CS reversed calpain activity values to the level of the saline treated group ($p<0.05$). Besides, the effect on caspase 3 and cathapsin B was more pronounced. Inhibition of cysteine proteases induced by treatment protocol was parallel with marked decrease in seizure severity. These results indicate that both antiepileptic drugs carbamazepine, levetiracetam act partially through the inhibition of cysteine proteases and that the calpain inhibitor, calpastatin might has an important role in the treatment of epilepsy.

Key words: Levetiracetam, calpastatin, calpain, caspase 3, cathapsin B

INTRODUCTION

Epilepsy which is one of the most common neurological disorders that may occur due to disturbances in the normal balance of excitatory and inhibitory neurotransmitters within the seizures focus in the brain (Lothman and Bertram, 1993; McNamara, 1994, 1999). Most behavioral signs and symptoms associated with seizures are related to the normal function of the affected region of the brain (Hauser and Hesdorffer, 1990). Accordingly, most seizures result from discharge, originating from cortical, subcortical and hippocampal structures (Avanzini and Franceschetti, 2003).

Levetiracetam is an atypical antiepileptic drugs that considerably differs from other novel antiepileptic drugs in that it does not interfere with any known target for anticonvulsant activity and appears to have alternative modes of action. In fact, the drug does not affect voltage-dependent channels or receptors for major inhibitory or excitatory neurotransmitters (Klitgaard and Pitkanen, 2003). It was proposed that it binds to a specific, as yet unidentified site on the synaptic plasma membrane (Noyer *et al*., 1995). Several pharmacological properties of LEV have been reported including binding to synaptic vesicle protein 2A (SV2A) (Lynch *et al*., 2004). In addition, inhibition of Ca^{2+} release from the inositol triphosphate (IP_3) sensitive intracellular storage sites (Fatatis *et al*., 1994; Cataldi *et al*., 2005). However, its precise mechanism of action is still not fully elucidated. Carbamazepine (CBZ), a traditional antiepileptic drugs; is widely used as a first-line drug in the management of tonic-clonic seizures. It blocks sodium channels during rapid, repetitive, sustained neuronal firing (Roger *et al*., 2004).

Corresponding Author: Abdulqader Alhaider, Departemt of Pharmacology, College of Medicine, King Saud University, P.O. Box 2925 Riyadh 11461, Saudi Arabia Tel: 00966 14671346 Fax: 0096614677200