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Pharmacological Upregulation of Glutamate Transporter 1 Improves Cognitive Deficits in an Animal Model of Temporal Lobe Epilepsy

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Background and Aim : Epilepsy has been one of the major mental disorders through centuries. It is defined as spontaneous recurrent seizures and is accompanied by many cognitive abnormalities including learning and memory. It is well described that one of the main mechanisms underlying these cognitive deficits is glutamate excitotoxicity. Astrocytes play an important role in the epileptogenesis process as the main glutamate scavengers. Excess glutamate can be cleared by GLT-1 glutamate transporters and thus excitotoxicity can be reduced. In this study, the effect of GLT-1 pharmacological upregulation on object recognition memory was assessed.

Methods : Male Wistar rats (200-280 g) were randomly divided into 4 groups (N=5): 1. Control group (received vehicle); 2. Pilocarpine group (temporal lobe epilepsy was induced using pilocarpine); 3. Pil+Cef group (animals received pilocarpine and 5 injections of Ceftriaxone 200 mg/kg); 4. Ceftriaxone group (receiving only 5 injections of Ceftriaxone 200mg/kg). Animal model was induced by an injection of lithium (127mg/kg) followed by pilocarpine i.p. administration (30mg/kg), 20 hours later. Ceftriaxone was injected 48 hours and 24 hours before and after pilocarpine (five consecutive days). Seizure behavior was monitored 3 weeks after model induction and animals showing spontaneous recurrent seizures were chosen for behavioral analysis. Object recognition memory was assessed using Novel Object Recognition Task. The test was carried out in three phases. In the habituation phase, the animals were placed in the apparatus for ten minutes. 24 hours later, during the acquisition phase, animals were placed along with the familiar object and were given 10 minutes to explore the objects. 90 minutes later, a test trial of 3 minutes was taken, during which the animal's exploration behavior towards familiar and novel object was evaluated using a video camera and ANY-Maze tracking software. Gene expression was evaluated using RT-qPCR for GLT-1 mRNA transcript. Hippocampus was extracted and homogenized and RNA was extracted using conventional Trizol method. cDNA was synthesized using random hexamer primers and gene expression was studied by SYBR Green qPCR. Data was analyzed using GraphPad Prism 7.0.

Results : Analyzing the results obtained showed that temporal lobe epilepsy can severely damage object recognition memory in Pilocarpine group compared to Control animals ($p<0.05$). Ceftriaxone treatment increased GLT-1

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expression ($p < 0.0001$) and significantly improved object recognition memory studied in NORT compared to animals in Pilocarpine group ($p < 0.001$). Exploration behavior was intact in all animals, showing that neither TLE induction, nor Ceftriaxone treatment do not affect this behavior.

Conclusion : TLE can increase excitotoxicity and consequently cause severe damage to hippocampus, the main center of learning and memory. In this study, it is demonstrated that decreasing glutamate excitotoxicity by targeting astrocytic glutamate clearance can reverse this damage. Further study is necessary to evaluate the therapeutic potential of this treatment on TLE cognitive defects.

Keywords : Epilepsy, learning, memory, GLT-1, astrocyte, NORT