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Stimulation of the anterior nucleus of the thalamus induces changes in amino acids in the hippocampi of epileptic rats

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ABSTRACT

We investigated the changes in the levels of amino acids during high frequency stimulation (HFS) of the anterior nucleus of the thalamus (ANT) in epileptic rats, which had seizures induced by unilaterally stereotactic administration of kainic acid (KA). Thirty-six adult male Wistar rats were divided into three groups: the KA-stim group (KA rats received ipsilateral ANT stimulation), the KA-sham group (KA rats received sham stimulation) and the control group, which underwent stereotactic administration of saline and received ipsilateral ANT stimulation. Microdialysis probes were unilaterally lowered into the CA3 region of the hippocampus, but probes were implanted bilaterally in the KA-stim group. The concentrations of glutamate (Glu), taurine (Tau), aspartate (Asp) and γ-aminobutyric acid (GABA) in the dialysate samples were determined by high-performance liquid chromatography. The concentrations of Glu, Asp and Tau in the hippocampi of KA rats were significantly higher than that found in control rats; however, no difference in the concentrations of GABA were found. In the ipsilateral hippocampi (KA-injected) of rats in the KA-stim group, stimulation of the ANT caused decreases in concentrations of Glu and Asp, an increase in the concentration of GABA and no significant change in the concentration of Tau. Unilateral ANT stimulation did not influence the amino acids in the contralateral hippocampus. In control rats, extracellular Tau significantly increased during and after stimulation. This study demonstrated that unilateral ANT stimulation inhibited the hyperactivation of the excitatory process and promoted the inhibitory process in the ipsilateral hippocampus of KA rats.

1. Introduction

Temporal lobe epilepsy (TLE) is the most frequent focal epilepsy and is often resistant to medications. The resection of mesial temporal structures can lead to the absence of seizures in more than 70% of patients (Cohen-Gadol et al., 2006). However, this type of surgery is not suitable for up to 30% of the TLE patients because a portion of patients' seizures originate in both temporal lobes or because some are at risk of substantial verbal memory loss after the surgery (Kwan and Brodie, 2000). Deep

Abbreviations: ANT, anterior nucleus of the thalamus; HFS, high frequency stimulation; KA, kainic acid; Glu, glutamate; Tau, taurine; Asp, aspartate; GABA, γ-aminobutyric acid; TLE, temporal lobe epilepsy; DBS, deep brain stimulation

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brain stimulation (DBS) is a form of non-resective, adjustable and reversible therapy that has been utilized for the treatment of epilepsy in recent years. Several institutes have published studies on small series of patients with ANT implants and have showed similar results; there was a significant reduction in the number of seizures of approximately 50% (Andrade et al., 2006; Lee et al., 2006; Lim et al., 2007; Osorio et al., 2007). These results culminated in a multicenter, double-blind, randomized trial (SANTE), which attempted to demonstrate the effectiveness of the bilateral ANT stimulation in patients with intractable epilepsy (Fisher et al., 2010). There was a 40.4% decrease in the median seizure frequency in the stimulated group compared with a 14.5% decrease in the control, no-stimulation group.

Nonetheless, the mechanism by which ANT–DBS decreases seizure frequency is still unclear. It is well-known that epileptic seizures can be produced by an imbalance between the excitatory (glutamate, aspartate) and inhibitory (GABA, glycine and taurine) neuronal transmitters (Szyndler et al., 2008; Morimoto et al., 2004). Previous studies have shown that the concentrations of amino acids were altered in epilepsy. Significant elevation of extracellular Glu has been found in the hippocampus of TLE patients (Wilson et al., 1996; Cavus et al., 2005). In animal models, disturbances in the local metabolism and the release of amino acids also occurred (Szyndler et al., 2008; Maciejak et al., 2009, 2010; Kanamori and Ross, 2011). In these studies, Glu and Tau increased, whereas GABA increased or decreased in different regions of the brain. It appeared that overactivity of the excitatory pathways and/or reduced activity of the inhibitory pathways constituted one of the crucial mechanisms involved in epileptogenesis and seizures. Although, whether ANT stimulation can attenuate these pathological pathways remains to be elucidated.

The KA-induced epileptic rat is a widely used animal model of TLE, which has been shown to most closely resemble the EEG, morphological and biochemical abnormalities of human TLE (Riban et al., 2002). After unilateral injection of KA into the hippocampus, the rat develops spontaneous, recurrent seizures within 90 day (Bragin et al., 2005). In this study, we evaluated the effects of unilateral ANT stimulation on the changes of amino acids in the hippocampi of epileptic rats induced by the stereotactic administration of KA. Intracerebral microdialysis was used to test the extracellular concentrations of Glu, Asp, Tau and GABA in the hippocampus.

2. Results

2.1. *Basal levels of amino acids*

Basal concentrations of Glu, Asp, Tau and GABA in the ipsilateral (KA-injected) and contralateral hippocampus of the KA rats and in the ipsilateral hippocampus (saline injected) of the control rats were analyzed (Fig. 1). There were no significant differences between the contralateral hippocampus of the KA rats and the control rats in the basal levels of Glu (0.188 ± 0.016 vs. 0.280 ± 0.021 μM, $p=0.07$), Asp (0.069 ± 0.009 vs. 0.059 ± 0.01 μM, $p=0.69$), Tau (1.43 ± 0.20 vs. 1.35 ± 0.26 μM, $p=0.83$) or GABA (0.124 ± 0.015 vs. 0.185 ± 0.012 μM, $p=0.30$). However, we observed significant increases in the basal levels of Glu (0.856 ± 0.056 μM, $p<0.01$), Asp (0.856 ± 0.056 μM, $p<0.01$) and Tau (0.856 ± 0.056 μM, $p<0.05$) in the ipsilateral hippocampus of the KA rats compared to the control group (Fig. 1a–c). There were similar results in the basal concentrations of Glu ($p<0.01$), Asp ($p<0.01$) and Tau ($p<0.05$) between the ipsilateral hippocampus and the contral-

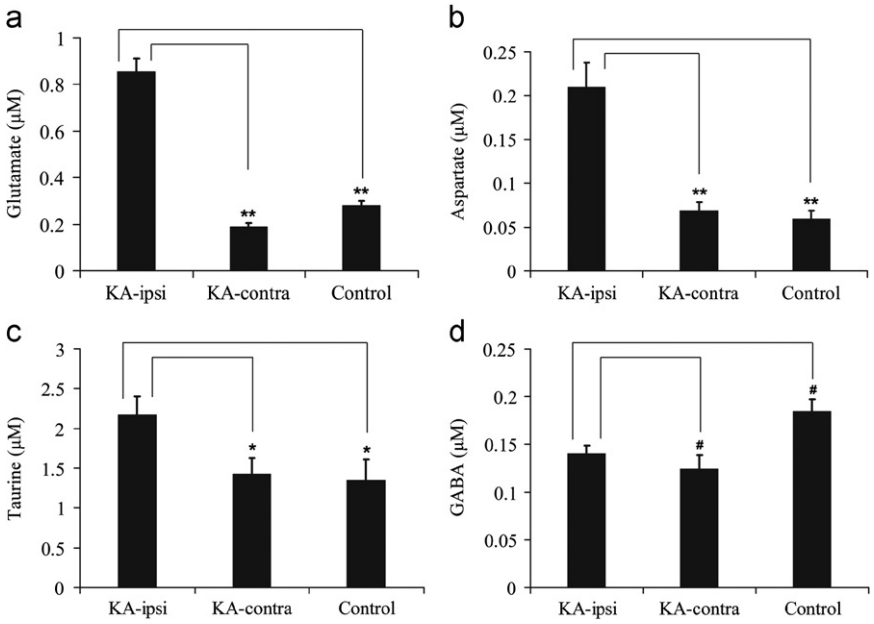

Fig. 1 – Basal levels of Glu (a), Asp (b), Tau (c) and GABA (d) were obtained from the first three dialysates before high frequency stimulation in ipsilateral and contralateral hippocampi of KA rats and in control rats. Statistical analysis was performed by one-way ANOVA followed by post hoc analysis using LSD test. The results are expressed as the mean±SEM; KA-ipsi, ipsilateral hippocampus of KA rats; KA-contra, contralateral hippocampus of KA rats; $^{\#}p>0.05$, $^{*}p<0.05$, $^{**}p<0.01$ vs. KA-ipsi.