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Deep brain stimulation of the anterior nucleus of the thalamus reverses the gene expression of cytokines and their receptors as well as neuronal degeneration in epileptic rats

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ABSTRACT

Background: Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) is effective in seizure control. However, the mechanisms remain unclear.
Methods: Sixty-four rats were randomly assigned to the control group, the kainic acid (KA) group, the sham-DBS group and the DBS group. Video-electroencephalogram (EEG) was used to monitor seizures. Quantitative real time PCR (qPCR) was applied for detecting interleukin-1 beta (IL-1β), IL-1 receptor (IL-1R), IL-6, IL-6 receptor (IL-6R), gp130, tumor necrosis factor-alpha (TNF-α), TNF-receptor 1 (TNF-R1) and TNF-receptor 2 (TNF-R2) expression 12 h after the establishment of an epileptic model. The neuronal structural degeneration in the hippocampus was evaluated with transmission electron microscopy (TEM) at this same time point.
Results: The seizure frequency was 48.6% lower in the DBS group compared with the sham-DBS group ($P < 0.01$). The expression of IL-1β, IL-1R, IL-6, IL-6R, gp130, TNF-α and TNF-R1 was elevated in both the KA and the sham group compared with the control group (all $Ps < 0.01$). Additionally, ANT-DBS was able to reverse this gene expression pattern in the DBS group compared with the sham-DBS group (all $Ps < 0.01$). There was no significant difference in TNF-R2 expression among the four groups. The neuronal structural degeneration in the KA group and the sham-DBS group was more severe than that in the control group (injury scores, all $Ps < 0.01$). ANT-DBS was also capable of relieving the degeneration compared with the sham-DBS group (injury score, $P < 0.01$).
Conclusions: This study demonstrated that ANT-DBS can reduce seizure frequency in the early stage in epileptic rats as well as relieve the pro-inflammatory state and neuronal injury, which may be one of the most effective mechanisms of ANT-DBS against epileptogenesis.

1. Introduction

Epilepsy is a chronic neurological disorder that affects 0.5–.0% of all people, approximately fifty million globally. Unfortunately, one-third of the newly diagnosed patients are refractory to existing medical management strategies (Lee et al., 2015). A large number of such patients with refractory epilepsy are not appropriate for traditional resective surgery or cannot get seizure control after traditional resective surgery due to incomplete resection of epileptic foci, multiple epileptic foci or foci near a functional region (Bonilha et al., 2012; Feis et al., 2013). Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS), a novel neuromodulation technique, has been performed to address these cases. Recently, a randomized, multicenter and double-blind trail was conducted by Salanova et al., which showed that the median percent of seizure reduction from the baseline was 41% in the first year and 69% in the 5th year (Salanova et al., 2015).

Despite its efficacy, the mechanisms of ANT-DBS are still under discussion. A previous study demonstrated that increased aspartate and glutamine and decreased GABA and taurine were normalized by ANT-DBS, suggesting the abnormal neurotransmitter levels

Abbreviations: ANT-DBS, deep brain stimulation of the anterior nucleus of the thalamus; KA, kainic acid; TEM, transmission electron microscopy; qPCR, quantitative real time PCR; TS, total seizure; PS, partial seizures; GS, generalized seizures.

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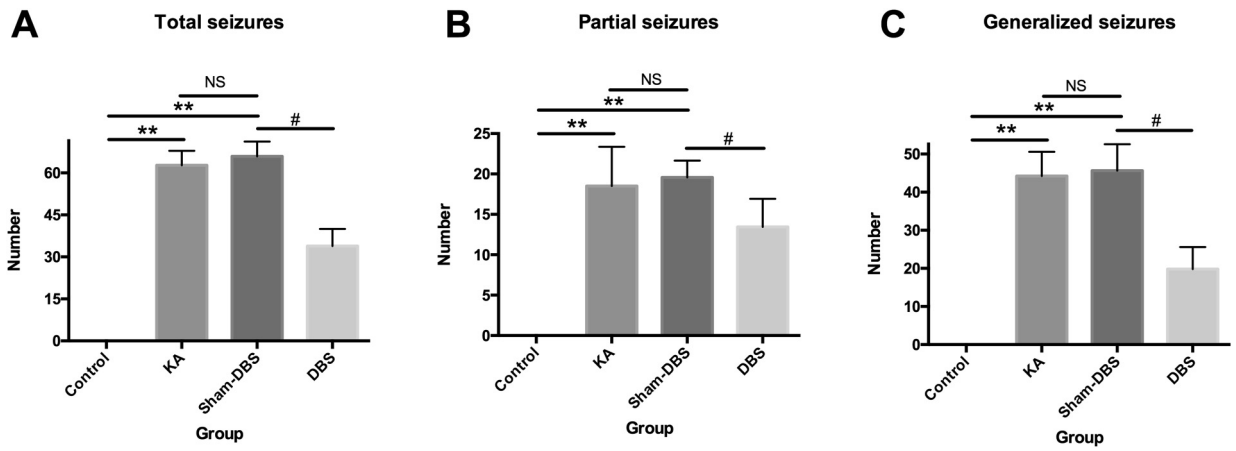

Fig. 1. Seizure frequency in the four groups (n = 16 for each group). **: P < 0.01, vs the control group; #: P < 0.01, vs the sham-DBS group; NS: no significant difference. A: Total seizures; B: Partial seizures; and C: Generalized seizures.

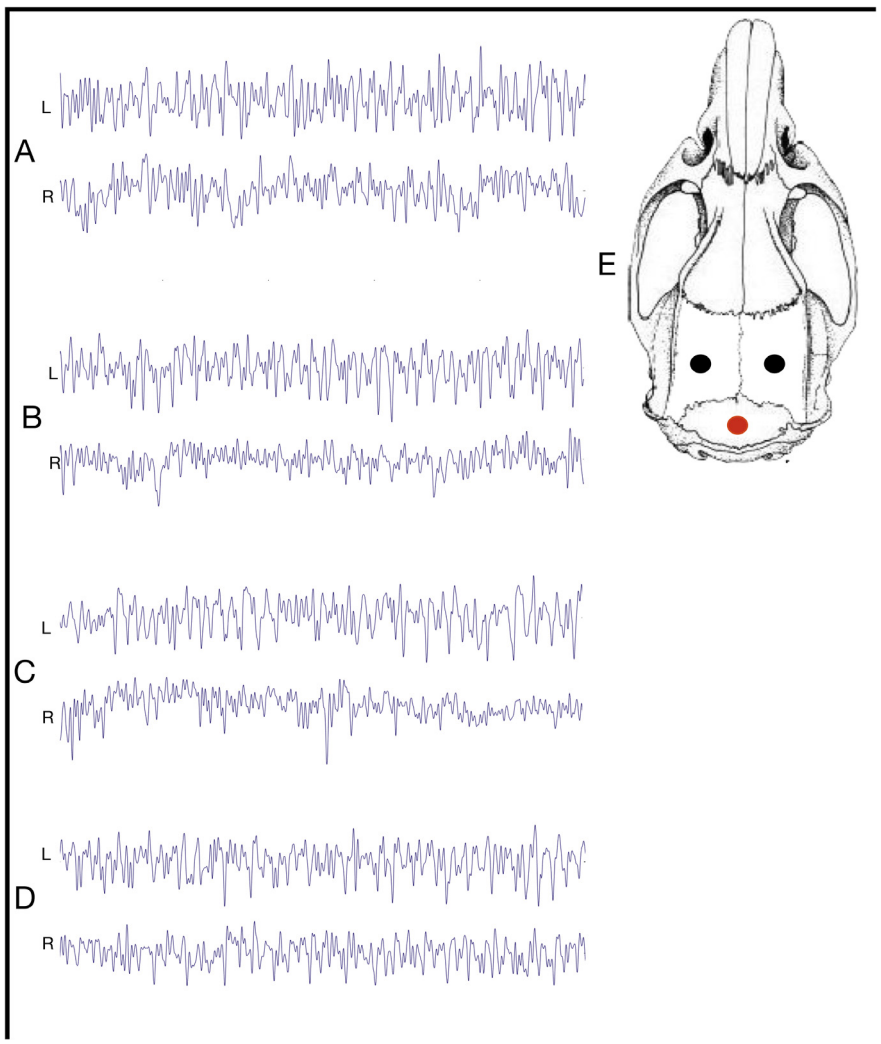

Fig. 2. A normal and similar EEG was observed in the bilateral hemisphere of the control group. The slow and asynchronous waves detected in the left hemisphere of the KA, sham-DBS group and DBS group. A: the control group; B: the KA group; C: the sham-DBS group; and D: the DBS group. L: left hemisphere; R: right hemisphere. E: Three anchor screws were used to record the EEG. The black dots were positioned on skull to record the EEG of the bilateral hemisphere. The red dot was set as the reference electrode.

involved in epileptogenesis were blocked (Shi et al., 2015). In addition, Selvakumar et al. found that the gene expression of brain-derived neurotropic factor (BDNF) was up-regulated, indicating that ANT-DBS may have a nourishing effect on the epileptic brain (Selvakumar et al., 2015). These studies concerning ANT-DBS were mainly performed in the chronic stage of epilepsy. However, the