Protective Effects of Anterior Thalamic Nuclei Stimulation on Hippocampal Neurons: A Promising Direction

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Introduction

Traditionally, patients with partial or generalized epilepsy resort to antiepileptic drugs for seizure control [1]. Albeit many new drugs and compounds have been invented, there are still a large number of patients with drug-resistant epilepsy whose seizures cannot be alleviated by drugs [2]. For these patients, seizure surgery is an apropos choice because some of them can achieve seizure freedom after surgery [3-5]. Many patients, however, are not candidates for resective surgeries for assorted causes, i.e., multiple epileptic foci, involvement of functional cortices, combination of major heart, brain or lung problems that fail general anesthesia, so they have to look for alternative therapies to cure their diseases [5,6].

Neuromodulation is an emerging treatment modality for diseases like epilepsy. Its basic idea is to stimulate specific regions of the neurological system with some forms of power to influence the neural circuit activity, i.e., electricity, light, magnetic force, ultrasound, which may result in various effects including a decrease in seizure frequency. The currently available neuromodulation methods include deep brain stimulation (DBS), vagus nerve stimulation, responsive neurostimulation and transcranial magnetic stimulation [7-9]. DBS has aroused increasing interest in the academic field, partly because of its success in the treatment of Parkinson’s disease, and it is now being tested as an alternative antiepileptic method for epilepsy [10,11]. Various targets have been experimented with, including anterior thalamic nuclei (ATN), subthalamic nuclei, hippocampus, fornix, brainstem and cerebellum [8,9]. Among these targets, ATN is a promising one for epilepsy because it is an important relay point that has myriad of reciprocal connections with other parts of the brain, including neocortices, basal ganglia, limbic system, and brain stem [12,13]. Besides, the effects of ATN stimulation have been proved by several antecedent studies. In 1980, Cooper et al. first reported their experimental application of ATN stimulation in man [14,15]. Subsequently, ATN stimulation has been tested as an antiepileptic method in a number of clinical trials [16-21]. Most clinical studies showed positive antiepileptic results. Although the seizure reduction rate varied in different studies, ranging from 20-70% [16-21], its effectiveness on intractable epilepsy has been gradually established. Based on these pilot studies, Fisher et al. [22] conducted a multi-center, double-blind, randomized controlled clinical trial, i.e., the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) study. 110 participants with partial or generalized intractable epilepsy went through a long-term observation with bilateral ATN stimulation. Results showed that the 2 year seizure reduction rate was 56% [22], and that the 5 year seizure reduction rate was 69% [23]. On the other hand, in laboratory animal studies (rats, dogs and monkeys) the effects of ATN stimulation on chemical-induced epileptic models were also under investigation, and seizure inhibition was observed [24-31]. These findings suggested that ATN stimulation is antiepileptic and may be applied in epilepsy treatment.

While definite effectiveness is observed, our knowledge of the mechanisms underlying the antiepileptic effects of ATN stimulation is insufficient. In previous literatures, electrophysiological alterations induced by DBS were considered to be related to the mechanisms. In chemical-induced epilepsy models, decreased neuronal excitability caused by negative slow potential shifts was detected when high frequency DBS was initiated [32,33]. The reason why stimulation of ATN nuclei resulted in potential shift in a remote brain area was assumed to be associated with the depolarization inhibition through fiber connection between the two sites [34,35]. As is mentioned above, ATN is an important anatomical relay station in the Papez circuit which has bi-directional fiber connection with new cortex, the limbic system, basal ganglia and many other regions of the brain [12]. On the other hand, some studies focused on its influences on neurotransmitters and glucose metabolism, and found that ATN stimulation induced complicated modulation on neurotransmitters and glucose metabolism in epileptic animals [36-40]. We have also done research in this field. Our results showed that short-term and long-term ATN stimulation resulted in a decrease in the excitatory neurotransmitters and an increase in the inhibitory neurotransmitters [26,41], and that ATN stimulation inhibited glycolysis in epileptic animals, which were consistent with previous literatures [42].

Recently, we have further investigated the antiepileptic effects of ATN stimulation from histological and molecular aspects. We applied chronic ATN stimulation on the kainic acid-induced epileptic monkeys and rats, and observed a significant seizure reduction in these models [13,27,43]. Then we conducted immunohistochemical staining, including Nissl staining, NeuN staining and microtubule-associated protein-2 staining on the hippocampal slices to see if hippocampus could be influenced by ATN stimulation since it is a downstream structure in the Papez circuit relative to ATN. Results showed that ATN stimulation reduced the hippocampal neuronal loss, especially in the CA1-CA3 regions [13,27]. Molecular examinations were performed to detect alterations in the injury and apoptosis markers, i.e., heat shock protein 70, caspase-3, B-cell lymphoma-2, and Bcl2-associated X. Results showed that the hippocampal injury was attenuated by chronic ATN stimulation, which was in line with our pathological findings [13,27]. In temporal lobe epilepsy, progressive hippocampal neuronal loss occurred with the process of epileptogenesis [44]. In previous literatures, the hippocampal CA1 and
CA3 regions were considered to be more vulnerable to injuries [27,45]. In our studies, significant neuronal loss was observed in the CA1-CA3 regions. ATN stimulation reduced the neuronal loss, as revealed by pathohistological staining and molecular findings. These results demonstrated that chronic ATN stimulation is protective for the hippocampal neurons in epileptic animals. Such effects might be an important mechanism underlying ANT DBS in the treatment of epilepsy. However, there is still work to be done before we can confirm such protective effects exist in humans. Future studies should focus on more thorough evaluation of the potential protective effects, e.g. is chronic ATN stimulation accompanied by elevation of genes related to neuronal survival and decrease of genes related to neuronal apoptosis, is ATN stimulation associated with neuronal genesis, what are the direct effectors molecules of its protective effects? If answers to these questions can be found in future studies, then attempts to reverse epileptogenesis with ATN stimulation or other forms of neurostimulation might become worthwhile and reasonable.

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References