Inhibiting effect of vagal nerve stimulation to seizures in epileptic process of rats

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Abstract: Objective Our previous work suggested that sensitivity of hippocampal neurons is changed in process of epileptic activities, and closely parallel to the dynamic characteristic of epileptic activity of the neurons. This study investigated the sensitivity of epileptic brain to vagal nerve stimulation (VNS) in epileptic process. **Methods** Epileptic model was evoked by penicillin. Left vagal nerves were stimulated to inhibit the seizures induced by penicillin. The electrocorticography (ECoG) and electromyography (EMG) were recorded to analyze inhibiting effect of VNS in epileptic process. **Results** It was found that VNS could inhibit the seizures caused by penicillin, and the inhibiting effect of VNS to seizures increased as the vagal nerve stimulating time prolonged. It was also found that the inhibiting effect of VNS to seizures decreased in epileptic process. **Conclusion** The results suggested that the sensitivity of epileptic brain to VNS was different in epileptic process. The inhibiting effect of VNS to seizure decreased as the development of seizures.

Keywords: epilepsy; vagal nerve stimulation; chaos

1 Introduction

In recent years, vagal nerve stimulation (VNS) has been proposed as a possible way to improve the control of refractory seizures. To date, however, there is no complete understanding of the mechanism for this action nor any available guidelines or criteria for this kind of neuromodulating surgery^[1]. The inhibiting effect of VNS to epilepsy is different among patients. Even to same patient, inhibiting effect of VNS is changeable in different time. Neurons involved in epileptic processes exhibit high frequency discharges, which was scarcely modulated by physiological brain activity^[2]. With the development of chaos theory, it became clear that the activity of neurons containing deterministic chaos was important in brain function^[2,3]. Non-linear deterministic dynamics was found in the epileptic process^[5]. The spatio-temporal dynamics of epileptic activity change significantly in the epileptic process^[6,7,15,16].

In our previous research, we found that sensitivity of dorsal root ganglion (DRG) neurons to stimulus may depend on deterministic chaotic feature of neurons' firing series^[8]. The sensitivity of hippocampal neurons is closely parallel to the dynamic characteristic of epileptic activity of the neurons^[9]. Because the dynamic feature changes in the epileptic process, we reasoned that sensitivity of epileptic brain to VNS was different in epileptic process. In order to prove our hypothesis, we compared the inhibiting effect of VNS to seizures in the process of epileptic activity in rats.

2 Materials and methods

2.1 Animal and surgery Adult male Sprague-Dawley rats, weighing approximately 250 g, were used. The rats were anesthetized with ketamine (100 mg/kg, i.p.) and undergone a tracheotomy. The bone overlying the left frontoparietal cortex was removed, and the dura mater was retracted to expose the left frontoparietal cortex. The electrode was placed at cortical surface to record the electrocorticography (ECoG), and the electrode was inserted at right hind limb to record the electromyography (EMG). The induction of epilepsy by intracortical injection of penicillin (500 IU) into the left sensorimotor cortex^[10]. The epileptiform activity was

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analyzed by ECoG and EMG.

2.2 vagal nerve stimulation Left vagal nerve in neck was exposed, and the electrode was placed at left vagal nerve. The vagal nerve stimulation parameters are as followed: amplitude 10 V, rate 20 Hz, pulse width 120 μ s, stimulating time 10–40 s.

3 Results

3.1 The epilepsy was induced by penicillin After the injection of penicillin (500 IU) into the left sensorimotor cortex 5–20 min later, the seizures were observed at the right side of rats. The ECoG of left sensorimotor cortex and EMG of right hind limb were recorded (Fig. 1).

3.2 The inhibiting effect of VNS to epileptiform activity The inhibiting effect of VNS on EMG caused by sei-

zures was studied in 8 rats. After stimulating vagal nerve for 10 to 40 s, the EMG of right hind limb caused by seizures was inhibited completely by VNS. The inhibiting time of VNS on muscular activity increased from (9 ± 2.3) , (23 ± 3.1) to (45 ± 3.5) s as the stimulating time increased from 10, 20 to 40 s. So, The inhibiting effect of VNS to seizure increased gradually as the stimulating time increased ($n = 8$, $P < 0.01$; t -test; Fig. 2).

3.3 The different inhibiting effect of VNS to epilepsy in the process of seizure We compared the inhibiting effect of VNS (amplitude 10 V, rate 20 Hz, pulse width 120 μ s, stimulating time 10 s) on EMG caused by seizures of 12 rats in the process of seizures. The inhibiting effect of VNS on seizures was different in the process of seizure. The inhibiting effect of VNS was greater at onset of seizure. As the

Fig. 1 ECoG and EMG in epileptic rat model. **A:** ECoG of rat before and after penicillin injection. **B:** ECoG and EMG of seizure induced by penicillin.

Fig. 2 The inhibiting time of vagal nerve stimulation (VNS) to EMG caused by seizures. The inhibiting time of VNS to seizures increased gradually as the stimulating time of VNS increased from 10 s to 40 s ($*P < 0.01$, t -test). The arrows show the time points of VNS.

Fig. 3 Effect of VNS (10 s, indicated by bar) on EMG of right hind limb in epileptic model induced by penicillin. A: The inhibiting effect of VNS to EMG was greater at onset of seizure. B: Effect of VNS decreased in the middle of seizure.

Fig. 4 The inhibiting effect of VNS in the process of seizure. A: The firing rate histogram of EMG on right hind limb. Effect of VNS (10 s, indicated by bar) on EMG decreased in the process of seizure. B and C: the summary of effects of VNS on 12 epileptic rats. The inhibiting percent (B) and inhibiting time (C) of VNS decreased in the process of seizure ($*P < 0.01$, t -test).

seizures continued, they were getting serious. The inhibiting effect of VNS on seizures decreased as the development of seizures (Fig. 3). The inhibiting effect of VNS to epileptic activity decreased in the process of seizures ($P < 0.01$, t -test; Fig. 4).

4 Discussion

VNS is one of the important ways to control the refractory epilepsy. For one third refractory epilepsy patients, VNS was responded very well and the seizures were nearly controlled. For other one third patients responded to VNS, the seizures were reduced more than one half. However, the rest patients almost did not respond to VNS^[12]. So the effect of VNS is different among the patients. The inhibiting effect of VNS to epilepsy is depend on many factors, for example the parameters of VNS, the EEG patterns, the seizure patterns^[1,12]. In our result, we found that VNS had inhibiting effect on the seizures induced by penicillin, the inhibiting effect was increased as the increase of vagal nerve stimulating time. The inhibiting effect of VNS was different in the process of epilepsy. At the onset of seizures, VNS had significant inhibiting effect on seizures. As the seizures continued, they were getting serious but the inhibiting effect of VNS on seizures was decreased gradually. So, to same VNS, the sensitivity of brain was different in process of seizure.

Neurons involved in epileptic processes exhibit high frequency discharges and synchronization, which was scarcely modulated by physiological brain activity. The epileptic neuron has a stereotypic and synchronized electrical response called the paroxysmal depolarizing shift (PDS), which followed by an afterhyperpolarization, consists of a sudden, large, long lasting (50-200 ms) depolarization triggering a train of action potentials^[2]. With great progress made in non-linear dynamics science, non-linear deterministic dynamics was found in EEG and in epileptic process^[5,13,14]. The spatio-temporal dynamics of epilepsy processes transitions from high to low-dimensional system states, representing symptomatic synchronization phenomena of the activity of neurons involved in epileptic process^[5]. In our previous study, we found that the dynamic characteristic of hippocampal neurons' activity changed in the process of epileptiform activity. Degree of chaos of discharges in hippocampal neurons decreased in the process of epileptiform activity. So, the degree of chaos and complexity of EEG reduced in the epileptic process.

Based upon the changing in dynamical properties of EEG signals, it was reported to perform a seizure warning system^[15,16]. In our previous research, we found that sensitivity of DRG neurons to stimulus may depend on deterministic chaotic feature of neurons' firing series^[8,14]. The sensitivity of hippocampal neurons is closely parallel to the dynamic characteristic of epileptic activity of the neurons^[9]. The results in this study showed that sensitivity of epileptic brain to VNS changed in process of epileptic activity. This supported our hypothesis that the sensitivity of neurons to stimulus may depend on deterministic chaotic feature of their firing dynamic system^[8]. This hypothesis may be of help in understanding the basic nature of chaotic behavior in epileptic activities and eliciting new clinical strategies. The results of this research proved that the sensitivity of brain is not invariable and it may be changed as the dynamic change of the brain activities. If we can monitor dynamic activity of brain, evaluate the sensitivity of brain to VNS or antiepileptic drug, and perform a seizure warning system^[6,15,16], we can control the seizure when brain is much more sensitive to VNS or antiepileptic drug. This might be more effective way to control the seizure.

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癫痫发作过程中迷走神经刺激对癫痫的抑制作用

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摘要: 目的 我们以前的研究发现大鼠海马神经元对刺激的敏感性在癫痫发作过程中是变化的, 并且与神经电活动的非线性动力学特征密切相关。本研究观察在癫痫发作过程中迷走神经刺激(vagal nerve stimulation, VNS)对癫痫的抑制作用。**方法** 在青霉素诱导的大鼠癫痫模型上, 通过记录皮层脑电图和下肢肌电图观察癫痫发作情况, 电刺激左侧颈部迷走神经, 观察 VNS 对癫痫的抑制作用。**结果** VNS 对癫痫活动有明显的抑制作用, 其抑制作用随着刺激时间的延长而增加; 同时发现 VNS 对癫痫的抑制作用在癫痫发作过程是不同的, 癫痫发作开始阶段 VNS 的抑制作用较强, 随着癫痫发作的发展, 其抑制作用逐渐减弱。**结论** 大鼠癫痫发作过程中大脑对 VNS 的敏感性是不同的, 随着癫痫的发展, VNS 对癫痫的抑制作用逐渐减弱。

关键词: 癫痫; 迷走神经刺激; 混沌