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Antiepileptic effects of electroacupuncture vs vagus nerve stimulation on cortical epileptiform activities

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Abstract

Introduced about two decades ago, vagus nerve stimulation (VNS) therapy has been increasingly used for the treatment of refractory epilepsy recently. This study was set out to compare the effects between VNS and electroacupuncture (EA) on pentylenetetrazole (PTZ) induced epileptiform activities in the rat cerebral cortex. Under general anesthesia, the parietal cortex of the rat ($n=20$) was exposed to record the cortical epileptiform activities. The left vagus nerve was stimulated at 30 Hz, 1 mA or 3 mA for 5 min. For EA, "Dazhui" acupoint (GV14) was stimulated with a pair of acupuncture needles with the same parameters. The results show that both VNS and EA at either 1 mA or 3 mA could inhibit the PTZ-induced cortical epileptiform activities, and higher stimulation (3 mA) was not associated with a greater inhibition. In the cases that showed inhibitory responses, there were no statistically significant differences between the two modalities, implying that EA could be comparable to VNS in the treatment of epilepsy. Thus, under current experimental settings, the antiepileptic effect induced by electrical stimulation appeared not vagal specific, and EA could be a good alternative to VNS in the management of epilepsy.

Keywords: Epilepsy; Vagus nerve stimulation; Electroacupuncture; Cortex; Pentylenetetrazole; Rat

1. Introduction

Epilepsy is the most common primary disorder of the brain, second only to depression as a leading cause of neuropsychiatric disability worldwide. Though many (~60%) epilepsy patients can be effectively treated by antiepileptic drugs (AEDs), the remaining cases are insensitive to the current AEDs, classified as intractable epilepsy and often require invasive or surgical interventions.

Since approved by Food and Drug Administration of the United States in 1997, vagus nerve stimulation (VNS; Cyberonics, Texas, USA) has been increasingly used in recent years for the treatment of epilepsy in the developed countries. By employing electrical stimulation on the left cervical vagus nerve truck, chronic VNS has been reported to improve epileptic conditions in about two thirds of patients [1]. However, it is an expensive and invasive procedure that may have potential side-effects and complications, and needs to be used with caution.

The exact antiepileptic mechanisms of VNS are still unclear. It has been speculated that VNS desynchronizes electrical activities of the brain [2]. A recent study has shown that chronic VNS can indeed reduce the synchronization of theta frequency (6 Hz) but enhance the spectrum and synchronization of gamma bands (20–50 Hz) in EEG recording [3].

Although VNS may alleviate seizure in some of epileptic patients, it remains questionable whether the antiepileptic effect is specific to the vagus nerve, as electrical stimulation of the trigeminal nerve [4] or the great auricular nerve [5] may achieve a similar or even better result in relieving seizure attack in experimental rats. Thus, it has been speculated that the seizure reduction resulting from nerve stimulation is mediated

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by activating a non-specific "arousal" system in the brain [2]. It may be reasonable to propose that VNS works in a way that is not qualitatively different from other nerve stimulation procedures, though the implanted VNS device may provide an easy control and convenience to the patients. As the vagus nerve has a broad projection in the brain, VNS may be more effective than other methods of nerve stimulation. However, considering the importance of the vagus nerve in maintaining body homeostasis and potential complications from VNS [6], we need to consider this invasive procedure with caution.

Acupuncture has been used to treat epilepsy in China since ancient time. There have been many reports that acupuncture, transcutaneous electrical nerve stimulation (TENS) and other alternative therapies may produce positive effect on epilepsy [7,8] though not every study agrees [9]. It has been observed that stimulation of auricular acupoints or the great auricular nerve in the rat could significantly depress the epileptic-like electrocorticogram and the seizure behaviors [5]. Acupuncture has been shown to affect cortical field potentials in epilepsy animal models [10]. Recent studies have shown that acupuncture might increase the concentration of inhibitory amino acids and/or decrease the concentration of excitatory amino acids [11,12], lower the contents of nitric oxide (NO) in the central nervous system (CNS) [34], and inhibit epileptiform discharges in the amygdala and hippocampus [13,14].

Despite the above evidence that the somatic stimulation including acupuncture may alter brain activities and induce antiepileptic effects, there has been no direct comparison so far for the effect and efficacy between EA and VNS in controlled experimental settings. In this study, we set out to investigate how effectively VNS and EA might interfere with the PTZ-induced epileptic activities respectively. The hypothesis to be tested is that EA is comparable to VNS in suppression of epileptiform activities of the cerebral cortex.

2. Materials and methods

2.1. Surgical preparations

Experiments were performed in 20 male Sprague–Dawley rats weighing 200–280 g after approval from the institutional research ethics committee. The animals were anesthetized by intraperitoneal injection of ketamine (40 mg/kg) and xylazine (4 mg/kg) and maintained with an intravenous infusion of the same agent (ketamine ~6 mg/kg/h and xylazine ~0.6 mg/kg/h). This anesthetic regime was chosen because it has relatively mild depression of cortical activities [15]. After intubation of the trachea, the left cervical vagus nerve was isolated from surrounding tissue by a soft plastic sheet, and placed on a bipolar platinum hook electrode for stimulation. Then the animal was fixed on a stereotaxic frame and the left parietal cortex was exposed by craniotomy. The cortex was protected with warm paraffin oil in a skin pool made from the scalp to avoid drying of the exposed area. Body temperature was maintained at ~38 °C by a thermostatically controlled heating blanket.

2.2. Epileptic model

Cortical epileptiform activities were induced by slow injection (within 2 min) of pentylenetetrazole (PTZ, Sigma, USA) via the jugular vein at 60 mg/100 g body weight [16]. Repeated injections with the same dose of PTZ were given when the epileptiform activities were dwindling, usually 1–2 h after the previous injection.

2.3. VNS and EA stimulation

For VNS, the electrical stimuli delivered from an isolated stimulator (A-M2100 system, USA) were applied to the left cervical vagal trunk via a bipolar hook electrode at low (1 mA) and/or high (3 mA) intensities at a fixed frequency of 30 Hz with 500 μs pulse width for 5 min duration. We selected 30 Hz because it is the frequency most often used clinically, and a previous study [17] in which depth recording electrodes was placed in the patient's left hippocampus showed that 30 Hz VNS might suppress the interictal epileptiform waves, whereas 5 Hz VNS could increase them.

For EA stimulation, a pair of stainless steel acupuncture needles separated by 2 mm were inserted about 5 mm deep into the skin at the location between the last cervical and the first thoracic vertebral spinous processes at the midline of the back, equivalent to human "Dazhui" acupoint on Governor Vessel (GV) that is one of the most commonly used acupoints for epilepsy treatment [18]. The EA stimuli were delivered by an EA stimulator (CEFAR ACUS II, Sweden) at low (1 mA) and/or high (3 mA) intensities for 5 min duration with a fixed frequency of 30 Hz (pulse width 450 μs).

VNS and EA were given randomly, that is, in some experiments the EA was given first, usually started with low intensity at 1 mA, and followed by VNS, and in others it was VNS first followed by EA.

2.4. Recording procedures

A silver ball microelectrode was used to record the field potentials of the left parietal cortex over the sensorimotor area. The cortical electrical activities were discriminated and captured using a data acquisition system (Powerlab, Australia).

At the start of each test, a 10 min continuous recording of the baseline activities was made. Then, PTZ was applied to produce large spiky epileptiform cortical activities that can be easily counted by using a window discriminator. The activities were averaged over a given period of time and the counts were expressed as Mean±SE.

The counts in a 10 min period post stimulation were compared with that of the background for the same duration immediately prior to the stimulation. The effect of the stimulation was calculated by the following equation: effect=$(B-A)/A$ where B was post stimulation response and A was pre-stimulation background activity. If the changes of the counts after stimulation were 10% more or less than the background