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Neuroprotective effects of vagus nerve stimulation on hippocampal neurons in intractable epilepsy

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ABSTRACT

Vagus nerve stimulation (VNS) and electroacupuncture (EA) at specific acupoints have both shown promising anticonvulsant effects in intractable epilepsy patients. The differences between these therapies are target selection and stimulation parameter modulation. It has been demonstrated that EA of the extremities results in stimulation of the VN and protection of hippocampus neurons, possibly by an anti-inflammatory response. Similarly, VNS can also suppress neural inflammatory responses, implying that VNS may protect hippocampal neurons against seizure-induced damage.

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Introduction

Epilepsy is a common chronic brain disorder and affects up to 1–2% of the general population around the world [1]. Despite recent advances in our understanding of the molecular and cellular basis of epilepsy and the development several new medications directed against these mechanisms, satisfactory seizure control remains elusive in 30–40% of patients. In the USA alone, there are at least 3,000,000 people with medically refractory seizures of partial onset [2]. While resection of an epileptic focus can be curative in the carefully chosen patient, many individuals are poor surgical candidates due to multifocal seizure origin or eloquent cortex near epileptic foci [3]. Moreover, resection has failed in some patients, and they continue to have seizures postoperatively [4]. For these patients, vagus nerve stimulation (VNS) is an attractive alternative. VNS was by approved by the US FDA in 1997 as an adjunctive treatment for epilepsy, and to date, VNS has been performed on more than 65,000 patients with pharmacologically resistant epilepsy [5–7]. Several clinical studies have reported that VNS significantly decreased the frequency of recurrent partial seizures in epilepsy patients [8–12]. However, the neurocellular mechanisms by which VNS decreases seizure frequency are still unclear. An antiepileptic effect of electroacupuncture (EA) at certain acupoints has been demonstrated in both experimental models and clinical studies [13–15]. EA studies on animal models of temporal lobe epilepsy (TLE) have demonstrated protection of hippocampal neurons against sclerosis [16]. Seizure suppression by EA is mediated by activation of VN afferent inputs [17,18] and the neuroprotective efficacy attributed to a anti-inflammatory response [16]. The therapeutic benefits of VNS against intractable epilepsy may also result in part from suppression of neural inflammation [19]. In light of the anti-inflammatory responses induced by both treatment modalities and the demonstrated hippocampal neuroprotection provided by EA, we propose that VNS also protects hippocampal neurons against damage associated with uncontrolled epilepsy.

Hypotheses

It has been shown that both VNS and EA at acupoints have anticonvulsant effects mediated by activation of the VN, while EA provides significant protection of hippocampal neurons in animal models of TLE [16]. Based on common neural targets (VN) and the anti-inflammatory response, we propose that VNS also protects hippocampal neurons against seizure-induced damage.

Evaluation of the hypothesis

Experimental and clinical evidence indicates that inflammatory responses contribute to the pathophysiology of seizure-induced brain damage [20–22]. Increasing evidence shows that persistent neuroinflammation such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) is implicated in the pathogenesis of seizures and hippocampal neuronal degeneration of TLE [23–25]. In animal studies, limbic seizures rapidly and transiently enhanced mRNA expression of the pro-inflammatory

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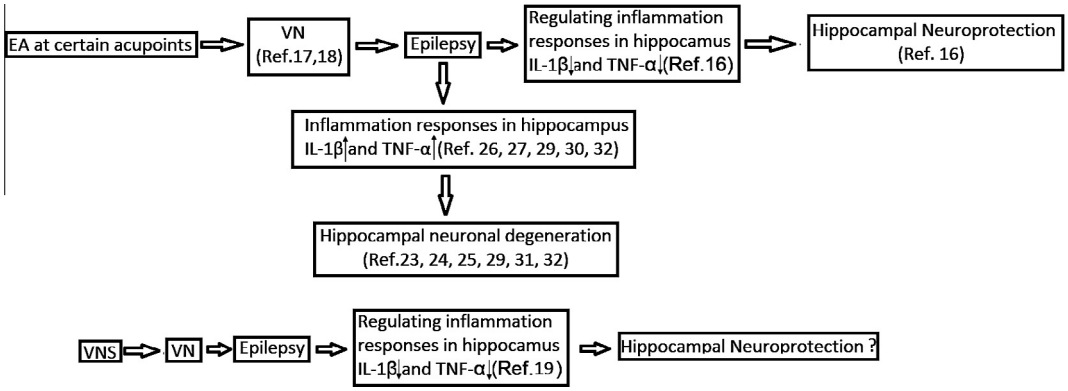

Fig. 1. Schematic illustration for antiepileptic effects of the electroacupuncture and vagus nerve stimulation and related anti-epileptic mechanisms. EA, electroacupuncture; Ref., reference (number represents related references); VN, vagus nerve; VNS, vagus nerve stimulation.

cytokines IL-1, IL-6, and TNF-α in the hippocampus, while direct intrahippocampal injection of IL-1β increased seizure activity [26,27]. In the kainic acid (KA) animal model of TLE, neuronal death results from a sustained inflammatory response [28] mediated by inflammatory cytokines such as interleukin-1β (IL-1β) and TNF-α [29]. IL-1β is a primary mediator of KA-induced hyperexcitability of hippocampal neurons [30] and plays a central role in KA-induced neurodegeneration [31], while neurotoxic TNF-α is known to increase in the hippocampus after KA administration [32]. Hippocampal neuroprotection in response to EA at HT8 has been suggested to be related to inhibit the expression of IL-1β and TNF-α in the hippocampus of KA-induced epilepsy rats [16]. It has been demonstrated that VNS also suppresses seizures in intractable epilepsy patients by regulating inflammation, with VNS causing decreases in the concentration of IL-1β and TNF-α [19]. Therefore, VNS may also protect hippocampal neurons in refractory TLE patients (Fig. 1).

Consequences of the hypothesis and discussion

No clinical study has yet shown that VNS can protect hippocampal neurons against epilepsy, so animal studies are warranted to provide a foundation for subsequent human neuroimaging trials. Such animal experiments must employ a validated model of TLE and confirm neuronal survival by means of Nissl and TUNEL staining. The design of experiment is as follows: thirty-six male rats were divided into three groups: control group (n = 12; rats received saline injections without implantation of the electrodes into the VN); KA group (n = 12; rats received KA injections without implantation of the electrodes into the VN) and VNS group (n = 12; rats received KA injections after undergoing electrodes implantation into the left cervical VN with the IPG on). One month after VNS, neuronal cell survival, the activations of microglia and astrocytes and mRNA expression of IL-1β and TNF-α were measured in the hippocampus. If VNS can significantly reduced the neuronal death, microglial and astrocyte activations and IL-1β and TNF-α in the hippocampus of VNS group compared with the KA group, the neuroprotective efficacy of VNS in the hippocampus will be confirmed. If the neuroprotective efficacy of VNS in the hippocampus is confirmed, VNS could help improve impaired cognitive function associated with hippocampal neurodegeneration in medically intractable epilepsy patients [33]. Moreover, VNS is a superior alternative to surgical resection for intractable epilepsy patients, and possibly also for drug-responsive patients who experience intolerable side effects. It has long been known that the early memory deficits observed in Alzheimer's disease (AD) are related to hippocampal degeneration as evidenced by structural and metabolic neuroimaging studies [34,35]. Therefore, VNS may also provide a feasible alternative treatment for AD.

Conflict of interest statement

None.

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