Epilepsy, electroacupuncture and the nucleus of the solitary tract

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Abstract
Vagal nerve stimulation and electroacupuncture have some promise as neuroprotective therapies for patients with poorly controlled epilepsy. It has been demonstrated that stimulation of acupuncture points on the extremities results in stimulation of the vagus nerve. It is possible that the antiepileptic effects of these two applications might be targeting the same centre in the brain. The nucleus of the solitary tract, which is a primary site at which vagal afferents terminate, is also the site for afferent pathways of facial, scalp and auricular acupuncture via trigeminal, cervical spinal and glossopharyngeal nerves. Taken together with laboratory findings, the neuroprotective pathways of electroacupuncture in epileptic models may stem from the collaboration of its anti-inflammatory and neurotrophic actions through the nucleus of the solitary tract via vagus nerve stimulation.

Keywords
Nucleus solitary tract, epilepsy, acupuncture.

Introduction
Epilepsy is a neurological disorder consisting of recurrent seizures resulting from excessive, uncontrolled electrical activity in the brain. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons in favour of a sudden onset of excitation. Treatment of epilepsy is successful in the majority of cases, but one third of epileptic patients are refractory to treatment. Temporal lobe epilepsy (TLE) is the most frequent form of pharmaco-resistant epilepsy in humans.¹

The amygdala, a temporal lobe structure that is part of the limbic system, has long been recognised for its central role in emotions and emotional behaviour. Pathophysiological alterations in neuronal excitability in the amygdala play a pivotal role in the pathogenesis and symptomatology of temporal lobe epilepsy.² Several lines of evidence point to the sclerotic hippocampus, rather than the amygdala or other temporal lobe regions, as the most likely origin of chronic seizures in TLE patients.³

The 'kindling' phenomenon has been employed extensively as a chronic model of temporal lobe epilepsy. Kindling is a phenomenon whereby provocation of focal seizures (most commonly using focal electrical brain stimulation) induces a clear progressive change in response over daily repetitions. This progression is readily apparent from all limbic and most forebrain stimulation sites, but it is most dramatic from temporal lobe structures, such as the amygdala and piriform cortex. With daily repetitions and the recruitment from the focus that precipitates the spread of seizures, kindling comes to model complex partial seizures with secondary generalisation and after many days of triggering kindled seizures by the experimenter, seizures begin to appear spontaneously without application of the kindling stimulus.⁴

Vagus nerve stimulation (VNS) treatment is a potential alternative therapy for patients with intractable epilepsy.⁵ A stimulating electrode is wrapped around the vagus nerve in the neck and a programmable pulse generator and battery pack are surgically implanted in the anterior chest wall. Although the precise mechanism of action of VNS is unknown, Ng and Devinsky reported a 57% reduction in seizure frequency with VNS.⁶
The dorsal vagal complex (DVC) is located in the dorsocaudal brainstem, in the floor of the fourth encephalic ventricle, and comprises the nucleus tractus solitarii (NTS), the area postrema and the dorsal motor nucleus of the vagus nerve (DMX). The NTS is the major recipient of afferent axons of the vagus nerve, from cardiovascular, respiratory and gastrointestinal sensory receptors, while the DMX contains the cell body of efferent vagal preganglionic neurons for visceral motor functions.

A growing body of evidence suggests that the central control of autonomic functions may involve experience-dependent plasticity of DVC neuronal networks. Functional synergy among the DVC nuclei is further potentiated by unusual diffusional properties of dorsal brainstem tissue: indeed, in neuroanatomical tract tracing studies tracers were found to diffuse away from an intra-NTS injection site throughout the whole DVC but not at all into the surrounding brainstem. At the cellular level, repetitive stimulation of afferent fibres leads to short or longterm depression of excitatory synapses in the NTS, while inhibitory inputs are potentiated.

Visceral relay neurons in the NTS regulate behaviour and autonomic reflex functions. The NTS is not only the site of vagal afferent projections, it also receives endings from glossopharyngeal, facial and trigeminal nerves. The NTS is also the recipient of several central afferent inputs. It is worth noting that most of the structures that receive a direct projection from the NTS project back to the nucleus. Direct projections from the cerebral cortex to the NTS have also been identified. Diverse inputs reach all the amygdala nuclei through the medial forebrain bundle whose fibres also originate from the NTS. Evidence from lesioning and tract tracing studies suggests that structural and functional links between the hippocampus and NTS projection neurons reinforce the potential importance of reciprocal communication between these brain regions.

It has been reported in the literature that all electroacupuncture types including body, facial and auricular point stimulation, have antiepileptic and neuroprotective effects for seizures.

Noguchi et al demonstrated that stimulation of acupuncture points on the extremitities resulted in the stimulation of the vagus nerve and the electroacupuncture specific response was not observed in rats after sciatic nerve denervation. Further, Shu et al demonstrated that the antiseizure effects of auricular electroacupuncture disappeared if the greater auricular nerve of rat was severed before electrical stimulation of the ear points.

**Hypothesis**

Since recent research has shown that recurrent epileptic seizures produce neurodegeneration in the amygdala and hippocampus in patients with poorly controlled epilepsy, focusing on the antiepilepsy mechanisms of vagal nerve stimulation and electroacupuncture have become more significant as possible antiepileptic therapies, and also as possible neuroprotective therapies that can also be used just after seizure for reducing inflammatory cytokines. It can be assumed that these two applications might have the same pathway or stimulate the same centre where the critical antiepileptic pathways originated. It would be valuable to consider the NTS as a neuroanatomical intersection centre for all the pathways of auricular, scalp, face, body acupuncture points and vagus nerve afferents at the level of the brainstem.

**Evidence and Discussion**

The NTS is a primary site at which vagal afferents terminate. Because afferent vagal nerve stimulation has been demonstrated to have anticonvulsant effects, it is likely that changes in synaptic transmission in the NTS can regulate seizure susceptibility. NTS stimulation interferes with the development of convulsive evolution and secondary generalisation.

It has been shown that limbic seizures rapidly and transiently enhance interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor alpha (TNFα) mRNA in the hippocampus, and intrahippocampal injection of IL-1β increased seizure activity. Brain cytokine mRNA levels are impacted by systemic cytokines. Increased serum TNFα and IL-1β results in an increase at the TNFα and IL-1β mRNAs in the NTS and hippocampus. Liu et al also reported that EA stimulation has a neuroprotective effect on the dopaminergic neurons by inhibiting the upregulation of the levels of TNFα and IL-1β mRNA in the substantia nigra.

It is worth noting that both VNS (vagus nerve outflow, which is cholinergic, i.e directed to macrophages and dendritic cells and interacts with nicotinic acetylcholine receptor, nAChR-a7, thereby
suppressing the synthesis of TNFα and IL-1β) and electroacupuncture can decrease serum TNFα and IL-1 levels via anticholinergic pathways. Furthermore, brain derived neurotrophic factor (BDNF) has been suggested to be involved in epileptogenesis. Laukkanen et al demonstrated that transgenic mice with decreased BDNF signalling have reduced epileptogenesis. On the other hand, several reports demonstrate that intrahippocampal infusion of BDNF can attenuate (or retard) the development of epilepsy. Moreover, real time polymerase chain reaction analysis showed that EA stimulation significantly restored BDNF mRNA expression in the hippocampus inhibited by immobilization stress. Although it has been shown that airway related vagal preganglionic neurons produce BDNF, there is no literature about the relationship between VNS and hippocampal BDNF levels.

Uvnas-Moberg et al demonstrated that gastrin and cholecystokinin release are stimulated by activation of sensory afferents originating in skin, subcutaneous tissue as well as in muscle; such effects are mediated via the vagal nerves. Known trigeminal to NTS connections can serve the facial acupoint stimulations directly to the NTS. Kobayashi et al also demonstrated that electrical stimulation of ethmoidal nerve resulted in stimulation of the NTS. Further, the results of another study by Imbe et al showed that the inflammation of the masseter muscle, a nociceptive stimulus of orofacial deep tissue, results in a widespread change in neuronal activity in the spinal trigeminal nucleus and NTS that depends in part on the integrity of the vagus. Thus, in addition to somatotopically organised nociceptive responses, orofacial deep tissue stimulation such as facial electroacupuncture is also coupled to somatovisceral and somatoautonomic processing that contributes to central neural activation. Auricular electroacupuncture can also stimulate the NTS via the auricular branch of vagus, trigeminal, glossopharyngeal and cervical spinal

Figure 1 Schematic illustration for anti-epileptic effects of the electroacupuncture and related neuroanatomical pathways (numbers represent the related references).
nerves. It has been shown that peripheral signals initiated by epinephrine influence the hippocampus via the NTS. Otake et al have demonstrated that afferents to the midline intralaminal thalamic nuclei issue collaterals to the general viscerosensory division of the NTS and these collaterals may coordinate changes in visceral reflex excitability and thalamocortical rhythms which are significant factors for epilepsy. NTS projections encompass thalamic nuclei that project topographically to the prefrontal cortex, hippocampus and ventral (limbic) striatum, regions activated by visceral stimulation.

Van Laere et al indicate that the thalamus, parahippocampal gyrus, hippocampus and amygdala were also deactivated by VNS. Further, electrical lesions in the bilateral caudal NTS can produce significant blockade of electroacupuncture induced sleep enhancement, which indicates a related mechanism to that of thalamocortical rhythms and cortical excitability. These extensive connections indicate that the NTS is a key structure for autonomic functions as well as for integration of somatic and autonomic responses and the excitability of specific brain regions. Moreover, animals with simultaneous stimulation of NTS and amygdaloid kindling which is an animal model of epilepsy produced by focal electrical stimulation of the amygdala did not reach the last stage VI, remaining in early stages I-III, and this finding provides a potential mechanism for the seizure protection obtained with electroacupuncture and vagal stimulation via the NTS.

Conclusion

This concept paper suggests that the NTS may be the centre of the antiepileptic effects of facial, scalp, auricular and body electroacupuncture via trigeminal, cervical spinal, vagal and spinal nerves respectively. Taken together, the neuroprotective pathways of all types of electroacupuncture in epileptic models may stem from the collaboration of its anti-inflammatory and neurotrophic actions through the NTS via vagus nerve stimulation.

Reference list


