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Vagus Nerve Stimulation has Antidepressant Effects in the Kainic Acid Model for Temporal Lobe Epilepsy

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ABSTRACT

Background: Depression is the most common psychiatric comorbidity in epilepsy patients. The lack of success with current pharmacological interventions for this patient population, highlights the importance of optimizing non-pharmacological neuromodulatory treatments such as vagus nerve stimulation (VNS). Studies on the antidepressant effect of VNS in epilepsy patients may be confounded by concurrent anti-epileptic drug therapy. To date, studies in epilepsy models overcoming this problem are lacking.
Objective: We investigated whether VNS affects anhedonia, a key symptom of major depression, in the kainic acid rat model for temporal lobe epilepsy.
Methods: Anhedonia was assessed in kainic acid (KA) and saline (SAL) injected rats using the saccharin preference test (SPT). To exclude differences in taste perception, the quinine aversion test (QAT) was performed. Both groups were randomly subdivided in a VNS and a SHAM group, yielding 4 experimental arms: KA-VNS, KA-SHAM, SAL-VNS and SAL-SHAM. Both VNS groups received 2 weeks of VNS, while the SHAM groups were not stimulated. Thereafter, the SPT and QAT were repeated.
Results: Saccharin preference was significantly reduced in the KA compared to the SAL rats ($P < 0.05$), without differences in quinine aversion. Two weeks of VNS significantly increased the saccharin preference in the KA-VNS group ($P < 0.05$), while it had no effect on quinine aversion. No effects of VNS or SHAM were found in the other groups.
Conclusion: The KA rats displayed anhedonia which was significantly decreased by VNS, indicating that this neuromodulatory treatment could likewise diminish depressive symptoms in patients suffering from temporal lobe epilepsy and comorbid depression.

Introduction

Depressive disorders are the most common type of psychiatric comorbidity in patients with epilepsy [1–3], especially in individuals suffering from refractory temporal lobe epilepsy [4–8]. Despite the availability of a variety of both anti-epileptic and antidepressant drugs, up to 30% of the patients fail to respond adequately to standard medication [9]. Furthermore, current treatment options for patients suffering both from epilepsy and depression are limited by the fact that anticonvulsant drugs can contribute to mood disturbances, while antidepressant drugs can increase seizure susceptibility [4,10,11]. The lack of success with current pharmacological interventions highlights the importance of optimizing non-pharmacological neuromodulatory treatments such as vagus nerve stimulation (VNS).

VNS consists of electrically stimulating the left vagus nerve at the cervical level by means of implanted electrodes and a programmable pulse generator. It is a well-established, safe and effective add-on therapy for the treatment of refractory epilepsy [12]. Clinical trials reported response rates (defined as the

Abbreviations: EEG, electroencephalogram; KA, kainic acid; mA, milliampere; QAT, quinine aversion test; SAL, saline; SPT, saccharin preference test; VNS, vagus nerve stimulation.

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fraction of patients with >50% reduction in seizure frequency) of 20–40% in the first year of treatment [13,14]. This response rate was shown to increase with time [15,16]. Furthermore, the anti-epileptic effect of VNS has been shown in numerous animal models for epilepsy [17–29].

The therapeutic effect of chronic VNS for treatment-resistant depression has been assessed in several open-label and long-term clinical studies in depressed patients without epilepsy [32–43]. VNS produced steadily increasing improvement of depressive symptoms with full benefit after 6–12 months and sustained efficacy during 2 years of follow-up [44]. Furthermore, these studies reported response rates (defined as the fraction of patients with >50% decrease in depression severity) of 30–40% and a remission rate of 15–17% after 3–24 months of treatment [45]. Unfortunately the only blinded sham-controlled clinical trial was inconclusive because some patients had not been adequately ramped-up and therefore did not receive the full therapy [32]. As for animal research, it has been shown that both acute [46] and chronic [47] VNS produce antidepressant-like effects in the rat forced swim test model [48]. The initial rationale for using VNS for the treatment of refractory depression was based on mood improvements in epilepsy patients treated with VNS, irrespective of the effects of VNS on seizure frequency [5,30,31].

To date, studies specifically addressing the antidepressant effects of VNS in epilepsy patients are lacking. Furthermore, such studies could be confounded by multiple factors, including anti-epileptic drug therapy, psychosocial, socio-economic and intellectual effects [8]. The use of animal models overcomes this problem and may be useful in identifying potential therapies for the treatment of depression in epileptic patients. This study aims at investigating the antidepressant potential of VNS in the kainic acid model for temporal lobe epilepsy with comorbid anhedonia.

Anhedonia, or the inability to experience pleasure [49], is a key symptom of major depression. Because pleasure is a subjective feeling, the DSM-IV operationally defines anhedonia as a diminished interest or pleasure in response to stimuli that were perceived as rewarding during the premorbid state [50]. In animal research, anhedonia can be assessed using the saccharin or sucrose preference test. This validated test for anhedonia is based on the rewarding properties of sweet substances, such as saccharin or sucrose solutions. Healthy animals have a strong inherent taste preference towards these sweet solutions, while animal models for depression show a significantly reduced saccharin or sucrose preference. This loss of taste preference reflects a decrease in reward sensitivity, i.e. anhedonia, which can be reversed by treatment with antidepressants [51–55]. To exclude the possibility that the reduced saccharin preference in our experiments is caused by a loss of taste due to the kainic acid, the induced status epilepticus or the subsequent neuronal loss, the quinine aversion test was performed.

Methods

A schematic overview of the study design is shown in Fig. 1. Rats were implanted with a VNS electrode and electroencephalogram (EEG) recording electrodes. After one week of recovery, half of the animals received intraperitoneal injections with kainic acid (KA) to induce status epilepticus. The other half of the animals was injected with matched volumes of saline (SAL). Both the KA group and the SAL group were randomly subdivided in a VNS group and a SHAM group, yielding 4 experimental arms: KA-VNS, KA-SHAM, SAL-VNS and SAL-SHAM. Anhedonia was evaluated 5 weeks after KA or SAL injections using the saccharin preference test. To control for loss of taste due to KA-induced status epilepticus, the quinine aversion test was performed. After this baseline testing, the VNS groups (KA-VNS and SAL-VNS) received 2 weeks of VNS, the SHAM groups (KA-SHAM and SAL-SHAM) were also connected to the set-up but were not stimulated. Subsequently, the saccharin preference test and the

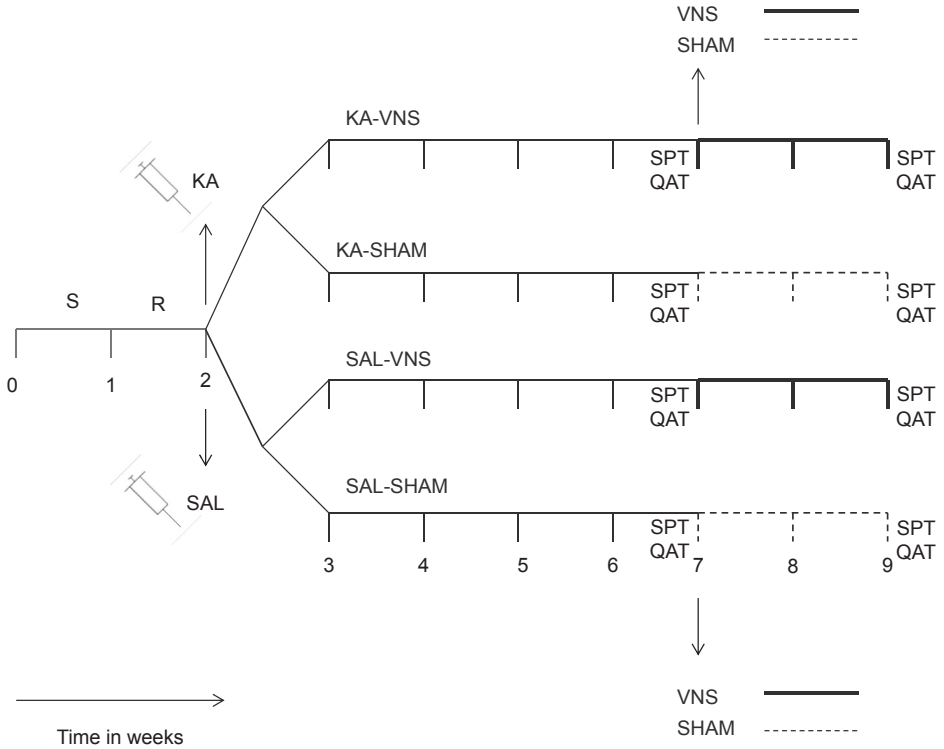

Figure 1. Schematic representation of the study design. S: surgery; R: recovery; SAL: saline; KA: kainic acid; SPT: saccharin preference test; QAT: quinine aversion test; VNS: vagus nerve stimulation.