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Review

Responsive neurostimulation for the treatment of medically intractable epilepsy

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ABSTRACT

With an annual incidence of 50/100,000 people, nearly 1% of the population suffers from epilepsy. Treatment with antiepileptic medication fails to achieve seizure remission in 20–30% of patients. One treatment option for refractory epilepsy patients who would not otherwise be surgical candidates is electrical stimulation of the brain, which is a rapidly evolving and reversible adjunctive therapy. Therapeutic stimulation can involve direct stimulation of the brain nuclei or indirect stimulation of peripheral nerves. There are three stimulation modalities that have class I evidence supporting their uses: vagus nerve stimulation (VNS), stimulation of the anterior nuclei of the thalamus (ANT), and, the most recently developed, responsive neurostimulation (RNS). While the other treatment modalities outlined deliver stimulation regardless of neuronal activity, the RNS administers stimulation only if triggered by seizure activity. The lower doses of stimulation provided by such responsive devices can not only reduce power consumption, but also prevent adverse reactions caused by continuous stimulation, which include the possibility of habituation to long-term stimulation. RNS, as an investigational treatment for medically refractory epilepsy, is currently under review by the FDA. Eventually systems may be developed to enable activation by neurochemical triggers or to wirelessly transmit any information gathered. We review the mechanisms, the current status, the target options, and the prospects of RNS for the treatment of medically intractable epilepsy.

Contents

Abbreviations: AD, afterdischarge; ANT, anterior nuclei of the thalamus; CMT, centromedian nucleus of the thalamus; CN, caudate nucleus; DBS, deep brain stimulation; ECoG, electrocorticogram; EEG, electroencephalogram; HFES, high-frequency electrical stimulation; MRF, mesencephalic reticular formation; PTZ, pentylenetetrazol; RBF, radial basis function; RNS, responsive neurostimulation; rPMC, right primary motor cortex; SANTE, stimulation of the anterior nucleus of thalamus for epilepsy; SLE, seizure-like event; STN, subthalamic nucleus; SUDEP, sudden unexpected death in epilepsy; VNS, vagus nerve stimulation.

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1. Introduction

Epilepsy is a common chronic neurological disorder that, with an annual incidence of 50 per 100,000 people, directly affects almost 1% of the world's population (Sander, 2003; Brodie et al., 1997; Sun et al., 2008). Despite a number of treatment options [*e.g.* pharmacotherapy, surgery, and vagus nerve stimulation (VNS)], many patients continue to suffer seizures. Uncontrolled epileptic attacks profoundly impact quality of life, with major disruptions to the familial, social, educational, and vocational activities of patients (Goldstein and Harden, 2000; Ettinger et al., 2010).

While seizure remission is achieved with antiepileptic medication in between 70% and 80% of epilepsy patients, the remainder, in whom symptoms are refractory to medications, currently have few alternative treatment options (Fridley et al., 2012; Sander, 2003). For these patients, one potentially curative option involves resection of the epileptic focus when it can be clearly delineated and safely resected (Wiebe et al., 2001). However, patients who have seizures arising from regions of the eloquent cortex, or which are multifocal, bilateral, or generalized, are not suitable for resective epilepsy surgery. Such intractable epilepsy, which cannot be resolved with drugs or surgery, is a significant public health problem that necessitates the development of alternative therapeutic approaches (Kahane and Depaulis, 2010).

One such approach involves electrical stimulation of the nervous system, which offers a reversible, adjunctive therapeutic option for patients with medically refractory epilepsy. Therapeutic stimulation can either be direct or indirect, involving, for example, the stimulation of brain nuclei or peripheral nerves, respectively. Three different approaches are supported by class I evidence: VNS (Handforth et al., 1998), stimulation of the anterior nuclei of the thalamus (ANT) (Fisher et al., 2010), and responsive neurostimulation (RNS) (Morrell, 2011). Of these, RNS is the most recently developed (Wu and Sharan, 2012; Kunieda et al., 2012). In the present article, we review the mechanisms, and current and future applications of RNS in the treatment of epilepsy.

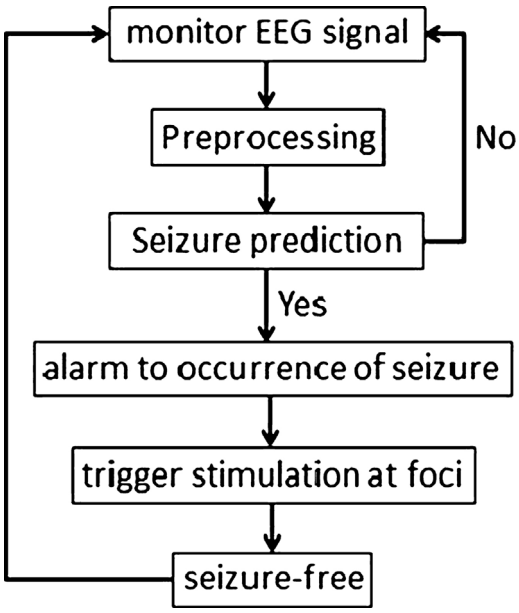

Fig. 1. The flow chart of the responsive stimulation system.

2. Stimulus mode of RNS

In epilepsy, because abnormal brain patterns emerge intermittently, the best solution would involve a closed-loop feedback control system, as in RNS, that does not affect other brain functions. The closed-loop RNS device was specifically designed to record electrographic activity using subdural and depth electrodes in order to detect nascent seizures and halt seizure propagation by stimulating the epileptic focus, thereby terminating the embryonic seizures before they become clinically apparent (Fig. 1) (Berényi et al., 2012).

The implanted closed-loop NeuroPace RNS system (NeuroPace, Mountain View, CA, USA) consists of a cortical strip lead, a programming system, a pulse generator, and a depth lead (Fountas et al., 2005). Responsive brain stimulation first involves implantation of subdural, or depth, electrodes in the target area, which are then connected to a small device that is implanted subcutaneously. Stimulation is delivered exclusively in response to seizure detection and relies on the programmed parameters (Fig. 2). Unlike traditional open-loop systems, the electrodes both record and stimulate: the implanted computer continuously monitors and records the electrocorticogram (ECoG) at the target, and, upon detection of an abnormal signal, the focal point is electrically stimulated in order to disrupt the abnormal activity. Empirical evidence supports its feasibility (Morrell, 2011; Fountas and Smith, 2007).

In the RNS system, one tool measures the length of the ECoG signal while another measures its area. The line length and area tools compare the recent average with the longer-term trend. When the activity within the recent window exceeds the average trend activity by a specified percentage, detection occurs. The line length tool is more commonly used to detect activity that does not diverge from the isoelectric baseline for significant time intervals but has a significant summed line length. On the other hand, the area tool is more commonly used for slower rhythmic electrographic seizure onsets that diverge from the baseline for longer periods of time and hence have large integrated areas. The half-way tool measures the duration and the amplitude of half-waves, which are defined as ECoG segments between relative maxima and minima. When the specified number of half-waves of the correct duration and amplitude are detected within a specified

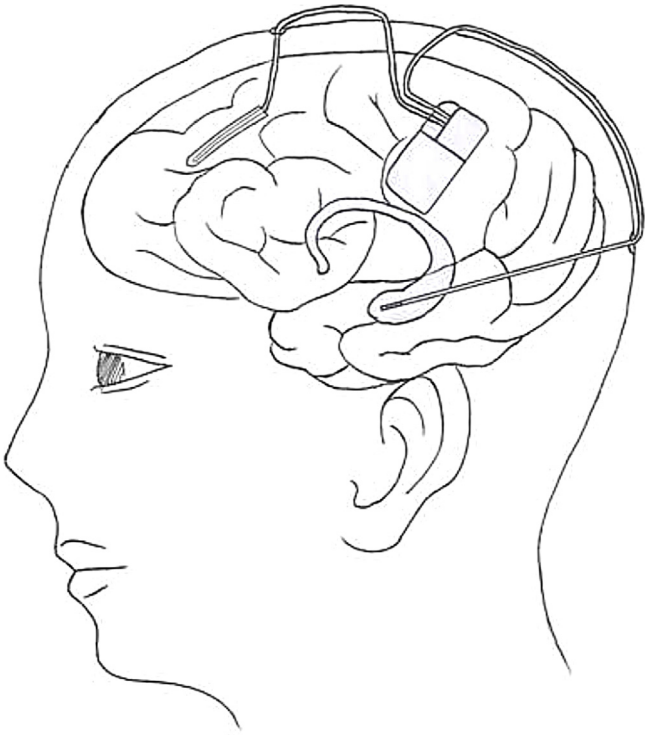

Fig. 2. The responsive stimulation system.