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Deep brain stimulation in epilepsy: what is next?

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Purpose of review

Experimental and clinical studies have suggested that epileptic seizures can be modulated or interrupted by electrical stimulations of subcortical structures that may exert a remote control on seizure generators. The aim of this review is to present these recent reports and to address the perspectives of this approach.

Recent findings

The use of deep brain stimulation to control several motor diseases has renewed the interest of this technique for epilepsy. Several neurology and neurosurgery groups have applied this therapy to drug-resistant forms of epilepsy for which resective surgery cannot be applied. The choice of the subcortical brain structures that are targeted strongly depends on the rationale that has been developed from experimental studies using animal models. The stimulation parameters and whether deep brain stimulation for epilepsy must be continuously applied or only when a seizure occurs are a matter of debate. This article discusses the use of stimulation of the cerebellum, caudate nucleus, anterior and centromedian nucleus of the thalamus, subthalamic nucleus, and substantia nigra to treat epilepsy, in light of recent and less recent clinical and experimental data.

Summary

New directions for studies are proposed for a better understanding of the mechanisms of action of this treatment.

Keywords

basal ganglia, cerebellum, review article, substantia nigra, thalamus

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Introduction

About 35% of epileptic patients do not respond to antiepileptic drugs [1], of whom perhaps one quarter may benefit from resective surgery. Patients who have seizures arising from eloquent cortex, or which are multifocal, bilateral, or generalized, are not candidates for resective surgery and can be considered for alternative therapy. For these patients, neurostimulation has a potential for benefit. Different approaches exist for treatment, depending on the brain region that is targeted and the way the stimulation is applied [2•,3•]. The aim is to reduce the probability of seizure occurrence and/or propagation, either by manipulating remote control systems (vagus nerve stimulation, deep brain stimulation) or by interfering with the epileptogenic zone itself (repetitive transcranial magnetic stimulation or direct cortical stimulation). In light of recent studies, we review the clinical and methodological perspectives of deep brain stimulation (DBS) as applied to a number of subcortical targets, including the cerebellum, different nuclei of the thalamus, and several structures of the basal ganglia system.

Is the cerebellum out of it?

From 1940 to 1970, cortical cerebellar stimulation was shown to have antiepileptic properties on different animal models of seizures [2•]. Because of this, assuming that cerebellar outflow was inhibitory, uncontrolled human studies were performed under the aegis of Irving Cooper [4]. These suggested that seizures could be modified or inhibited in a substantial number of patients [5]. These promising results, however, were not confirmed in three controlled clinical trials involving a total of 14 patients, of whom only two were improved [6–8]. Additional animal studies did not confirm previous experimental findings, and interest in using cerebellar stimulation for epilepsy faded, although the occasional study was conducted [9]. Recently, a double-blind, randomized, controlled, pilot study [10] conducted in five patients suffering from intractable motor seizures has renewed interest in cerebellar stimulation. Bilateral 10-Hz stimulation was applied to the upper medial surface of the cerebellar hemispheres, and parameters were adjusted to deliver a constant charge density of 2.0 $\mu C/cm^2$ per phase. During the initial 3-month, double-blind

phase, seizures were significantly reduced when the patients were stimulated. Over the following 6-month open-label phase, in which all the patients were stimulated, seizures were reduced by 41% (14–75%). The difference was significant for tonic and tonic–clonic seizures. Effectiveness was maintained over 2 years and few complications occurred.

Altogether, results of cerebellar stimulation appear contradictory, the target within the cerebellum (superior medial cerebellar cortex vs. cerebellar dentate nucleus) as well as the stimulation frequency (high vs. low) is uncertain, and the rationale for an antiepileptic effect remains to be determined.

The thalamus: how could we do without it?

Since the 1980s, different nuclei of the thalamus have been studied to understand the physiopathology of epilepsy because many pathways exist between thalamic nuclei and the cortex. Several thalamic targets have been stimulated to suppress seizures, mainly the anterior nucleus and the centromedian nucleus. There is limited proof from animal studies that stimulation of these structures can influence seizure threshold. However, clinical evidence exists showing that continuous stimulation of these targets in epileptic patients reduces seizure frequency and severity.

The anterior thalamus: a generator of seizures or a remote control system?

The anterior nucleus of the thalamus is central in the network that underlies limbic seizures and, as such, represents an attractive target for DBS in epileptic patients. Cooper and Upton [11] were the first to direct their interest to this nucleus based on the hypothesis that anterior nucleus could act as a 'pacemaker' for the cortex.

Animal studies later demonstrated that anterior nucleus was involved in the generation of pentylenetetrazol-induced seizures [12], that lesion of the mamillo-thalamic tract prevented pentylenetetrazol-induced seizures [13], and that 100-Hz electrical stimulation of anterior nucleus increased seizure threshold [14]. More recently, an anticonvulsant effect of high-frequency stimulation (HFS) was reproduced in other generalized and focal models of epilepsy [15–17]. HFS of anterior nucleus, however, was found to aggravate recurrent seizures in the kainate model of chronic epilepsy [18].

In epileptic patients, the effect of anterior nucleus HFS has been reported in four recent, open-label trials [19–22]. Overall, a 20–92% reduction of seizure frequency was observed, which was statistically significant in 12 of the 18 patients. One report showed that the insertion of electrodes by itself reduced seizures [21], one that the observed benefits did not differ between stimulation-on and stimulation-off periods [19], and one that the clinical benefit might increase after several years of stimulation [23]. Whether anterior nucleus stimulation might be more effective in temporal lobe epilepsy [24] remains an interesting issue.

Anterior nucleus stimulation has gained increasing interest during the last decade, and experimental data indicate some efficacy. Clinical results, however, appear less impressive, and the randomized, double-blind SANTE (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) trial, which is currently under investigation, should answer to the efficacy and safety issues of anterior nucleus HFS for partial onset seizures in human.

The centromedian thalamus: a target for generalized seizures?

In addition to the anterior nucleus, part of the intralaminar nuclei of the thalamus, the centromedian nucleus, has recently received both clinical and experimental interest. This nucleus is a part of the reticulothalamocortical system modulating cerebral cortex excitability and is known to participate in the control of vigilance states. Since the first open-label study conducted in five patients 20 years ago [25], Velasco *et al.* [26], as others [9], have accumulated data in patients suffering from different forms of seizures and epilepsies. The greatest benefits were obtained in patients with generalized tonic–clonic seizures and atypical absence of the Lennox–Gastaut syndrome in whom centromedian nucleus HFS induced a decrease of 80% of seizures, with a global improvement in their ability scale scores [27]. As for anterior nucleus stimulation, persistent antiepileptic effects were found at 3 months or more after discontinuation of the stimulation (i.e. 'off effect') [28]. By contrast, no improvements were found for either complex partial seizures or focal spikes in temporal regions [29], in agreement with a placebo-controlled study in seven patients with mesial temporal lobe epilepsy [30].

The efficacy of bilateral centromedian nucleus stimulation in generalized forms of epilepsies has been recently confirmed in four patients who were previously submitted to callosal section: seizure and interictal spiking frequencies were reduced by up to 95%, whereas attention level was increased in all patients [31].

Up to now, very few animal studies have examined the role of the centromedian nucleus or the five parafascicular nuclei of the thalamus – which have similar connections – in the control of epileptic seizures. In a genetic model of absence epilepsy in the rat (GAERS; Genetic Absence Epilepsy Rat from Strasbourg), pharmacological activation of the parafascicular nucleus was found to suppress spike and wave discharges [32]. More recently, 130-Hz

stimulation of this structure was reported to interrupt focal hippocampal seizures in a mouse model of mesiotemporal lobe epilepsy (M. Lanlois, P.O. Polack, H. Bernard, *et al.*, in preparation). Interestingly, a unique pattern of short synchronization of parafascicular nucleus neurons was found in this model, preceding the end of the hippocampal discharge. This suggests that the centromedian nucleus–parafascicular nucleus could play a role in the modulation of seizures.

Because of its unique location between cortical and limbic structures and the basal ganglia (see below), the centromedian nucleus/parafascicular nucleus nuclei could well possess a pivotal role in the remote control of seizures and be therefore an interesting target for DBS. More animal studies are clearly required to understand the role of this structure in the modulation of epileptic seizures.

The basal ganglia: it should work, but...

Since the beginning of the 1980s, experimental animal studies have suggested the existence of a 'nigral control' of epileptic seizures [33]. Indeed, inhibition of the substantia nigra pars reticulata (SNR) has potent antiepileptic effects in different animal models of epilepsy, and the GABAergic SNR output appears to be a critical relay in this control [34]. Local manipulations of the basal ganglia that lead to an inhibition of the SNR neurons (e.g. activation of the striatum or pallidum, inhibition of the subthalamic nucleus) also had significant antiepileptic effects [35], suggesting that different striato-nigral circuits are involved in the control of epileptic seizures. In humans, EEG, and clinical and imaging data also support the involvement of the basal ganglia in the propagation and/or the control of epileptic discharges [36]. This rationale has led to the first clinical proof-of-concept in Grenoble, in the late 1990s.

The caudate nucleus: a first approach of the basal ganglia remote control system

Following experimental evidence that stimulation of the caudate nucleus has antiepileptic properties in different animal models of seizures [2•], a few, uncontrolled, human trials started at the end of the 1970s [37], further suggesting the beneficial effect of striatal low-frequency stimulation (LFS) in a sizeable number of epileptic patients [9,38]. Bilateral LFS of the head of the caudate nucleus resulted in a significant decrease in both focal and generalized discharges [38], and some patients were even rendered seizure-free [9]. Epileptic activity was worsened by stimulating the caudate nucleus at a higher (50–100 Hz) frequency [38], a finding that was also reported in the aluminium hydroxide monkey model of motor seizures [39]. Therefore, if one assumes that LFS is excitatory and HFS inhibitory, then these clinical data – although suffering from lack of control protocol and from heterogeneity of the studied population – support the experimental findings that activation of the striatum inhibits the SNR through GABAergic projections and therefore leads to seizure suppression [35].

To date, the caudate nucleus is the only site of DBS for which, based on experimental and clinical data, LFS seems preferable than HFS. Although more than 50 patients have been stimulated so far, a more definitive evaluation of effect on seizure frequency is needed and controlled clinical trials are necessary.

The subthalamic nucleus: not really the same as for Parkinson's disease

In 1998, Vercueil *et al.* [40] showed that 130-Hz stimulation of the subthalamic nucleus (STN) interrupted absence seizures in the GAERS model of absence epilepsy. Since then, HFS of the STN has been reported to protect against seizures in different animal models [3•]. On the basis of these data as well as the rationale around the 'nigral control', the group of Grenoble University Hospital performed the first STN stimulation in a 5-year-old girl with drug-resistant inoperable epilepsy caused by a focal centroparietal dysplasia [41]. Later, 11 additional patients suffering from different forms of epilepsy received STN HFS at different institutions, with an overall reduction of seizures of at least 50% [42–44]. Good responders suffered from Dravet syndrome, Lennox–Gastaut syndrome, and progressive myoclonic epilepsy. In addition, bilateral stimulations were found to be more effective than unilateral ones [42], in agreement with experimental data [34]. Furthermore, whether the optimal target in epileptic patients is the STN itself or, as suggested in some patients [42,44], the SNR, remains an important issue (see below).

The interest for STN certainly comes from the fact that it is the most effective target to treat patients with Parkinson's disease with DBS. However, experimental and clinical data suggest that it may not be as effective in patients with epilepsy.

The substantia nigra pars reticulata: the output station of the basal ganglia

The possibility that seizures are controlled by the SNR emerged from several pharmacological studies in animal models, showing that direct or indirect inhibition of this structure suppresses very different types of seizures [35]. In addition, neuronal inhibition was found to be concomitant with the end of seizures using electrophysiological recording [45]. In this context, it was shown that DBS applied to the SNR also suppressed either generalized or focal seizures [3•]. In GAERS, the first parametric study [46] showed that bilateral, bipolar, and monophasic SNR stimulations at a frequency of 60 Hz and a pulse width of

60 μs are the optimal conditions to interrupt ongoing absence seizures without motor side effects. In addition, the threshold to interrupt epileptic seizures was lower in the SNR compared with the STN stimulation, in agreement with clinical data (see above). In human patients, a double-blind, cross-over, multicenter study is in progress in France (STIMEP) and aims at evaluating the clinical effect of DBS of the STN/SNR in patients with ring chromosome 20 epilepsy. These patients suffer from very long-lasting epileptic seizures, often evolving into status epilepticus, and are difficult to control with antiepileptic drugs. They exhibit a deficit of dopaminergic activity in the striatum as compared with normal individuals [47], a finding that is in accordance with the critical role of striatal dopamine in the control of seizures [35].

As the main output station of the basal ganglia, the SNR appears as a key structure in the control of epileptic seizures with both solid pharmacological and electrophysiological evidence. In addition, this structure could be a better target for DBS in epilepsy than STN, suggesting that the mechanisms involved in the suppression of seizures are different from those involved in motor control.

Scheduled vs. adaptive stimulation: treating epilepsy or seizures?

Most protocols that have evaluated DBS for epilepsy have used stimulation parameters derived from the literature on DBS for movement disorders. The leading idea was to reduce brain excitability and therefore to suppress conditions that favor the emergence of seizures. Accordingly, DBS has been mainly applied continuously, showing a potential benefit on seizure frequency in medically refractory epileptic patients. However, our recent experimental data suggest, in agreement with previous reports [40], that continuous stimulation may fail to control the occurrence of seizures, and that a refractory period of about 60 s exists during which any stimulation is without an effect [46,48]. Continuous stimulation of the SNR could even aggravate seizure occurrence, as also demonstrated for anterior nucleus stimulation [18]. Discontinuous scheduled DBS alternating 'on' and 'off' periods might, in part, alleviate this problem, although alternating protocols have been used in some human studies and appear less effective than continuous DBS [28]. On the contrary, limited, but growing data suggest that adaptive (i.e., seizure-triggered) stimulation might also be effective for seizure control in humans [2•,3•]. Such a strategy is distinct from continuous scheduled stimulation, as it aims at blocking seizures when they occur, rather than decreasing cortical excitability chronically. It requires an implanted stimulating device coupled with real-time signal analysis techniques, the stimulation being delivered following the automatic detection of an EEG change characteristic of the onset of ictal activity. Such an approach seems quite appropriate for the 'direct control' method with stimulation applied at the presumed source of seizures. Remote closed-loop stimulation, however, has been reported to decrease seizure frequency by 40.8% in four patients stimulated in anterior nucleus [49]. More studies in animal models are required to demonstrate the efficacy and advantage of a remote closed-loop device. A reduction of pentylenetetrazol-induced seizures was reported in rats by seizure-triggered trigeminal nerve stimulation, and adaptive DBS was more effective than the stimulation protocol involving a fixed duty cycle [50]. Currently, a new technology based on adaptive DBS to interrupt absence seizures in GAERS by SNR stimulation already provides encouraging data [48].

The use of adaptative DBS, rather than continuous DBS, is motivated by the paroxysmal nature of the seizures, the existence of refractory periods during chronic stimulation, the possible aggravation by continuous stimulation, and the reduction of power consumption with prolongation of battery life. It has the disadvantage of appearing more as an antiseizure treatment than as an antiepileptic one and requires the development of reliable automatic detection of seizures and optimal stimulation parameters.

Conclusion

As a conclusion, each author gives his own point of view according to his expertise as a neurologist (P.K.) or a biologist (A.D.).

According to the 'humanologist' point of view, DBS, whatever the target, has appeared to be safe and of potential benefit in treating medically intractable epilepsies. It has the advantage of reversibility and adjustability but remains palliative, so that surgical resection remains the gold standard treatment for drug-resistant epilepsies whenever this option is possible. Published controlled studies are few, and the number of enrolled patients is small. Therefore, DBS must be considered as experimental. Results, although encouraging, do not allow us to favor one DBS target, and indications might depend on the epilepsy type. Reduction in seizure frequency appears similar to that observed for other neurostimulation procedures (cortical stimulation, vagus nerve stimulation), and large-scale, controlled, clinical trials comparing different stimulation protocols are needed. This should permit identifying seizure types and epilepsy syndromes, which may respond to stimulation, as well as defining the types of stimulation likely to be efficacious. This requires improving our knowledge of the neural circuits in which seizures start and propagate, of the mechanisms by which neurostimulation has its effect,

and of optimal stimulation parameters. The development of experimental research in this field and rigorous evaluation are essential to improve clinical efficacy.

The 'ratologist' point of view

According to the 'ratologist' point of view, the main concern with DBS, not only in epilepsy but also in other diseases, is that we still know very little about its mechanisms of action. It appears obvious that these mechanisms or circuits differ from one pathologic entity to another, even if the target is the same. In this respect, different targets and stimulation parameters are likely necessary for different forms of epilepsy. The lack of reliable animal models for drug-resistant forms of epilepsy is a major obstacle. In addition, whether HFS is really 'inhibitory', imposes a frequency incompatible with seizure frequency, or acts by retrograde activation remains to be determined. New technologies [51] will be of great help. Finally, the use of DBS in the treatment of epilepsy requires a better understanding of the possible 'endogenous' control circuits that exist in the central nervous system, how they develop along with epileptogenesis, and how they could be better utilized to increase a patient's quality of life.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 201).

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