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Original Articles

Effect of Subthalamic Nucleus Stimulation on Penicillin Induced Focal Motor Seizures in Primate

S. Prabhu [a,b], S. Chabardès [a,b,c], A. Sherdil [a,b], A. Devergnas [b], S. Michallat [b], M. Bhattacharjee [a,b], H. Mathieu [d], O. David [a,b], B. Piallat [a,b,*]

[a] Univ Grenoble Alpes, GIN, F-38000 Grenoble, France
[b] INSERM, U836, F-38000 Grenoble, France
[c] CHU de Grenoble, Hôpital Michallon F-38000 Grenoble, France
[d] UMS IRMaGe, F-38000 Grenoble, France

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ABSTRACT

Background: Drug-resistant motor epilepsies are particularly incapacitating for the patients. In a primate model of focal motor seizures induced by intracortical injection of penicillin, we recently showed that seizures propagated from the motor cortex towards the basal ganglia.
Objective: Using the same animal model here, we hypothesized that disruption of subthalamic nucleus (STN) activity by chronic high frequency stimulation (HFS) could modify pathological excessive cortical synchronisation occurring during focal motor seizures, and therefore could reduce seizure activity.
Methods: Two monkeys were chronically implanted with one electrode positioned into the STN. In each experiment, seizures were induced during 6 hours by injecting penicillin into the motor cortex. During stimulation sessions, HFS-STN was applied at the beginning of penicillin injection.
Results: Our results indicate that HFS-STN improved focal motor seizures by delaying the occurrence of the first seizure, by decreasing the number of seizures by 47% and therefore the total time spent seizing by 53% compared to control. These results argue for a therapeutic use of HFS-STN in motor seizures because they were obtained in a very severe primate model of motor status similar to that seen in human. Furthermore, HFS-STN was much more efficient than direct cortical HFS of the epileptic focus, which we already tested in the same primate model.
Conclusions: The present study suggests that HFS-STN could be used as an experimental therapy when other therapeutic strategies are not possible or have failed in humans suffering from motor epilepsy but the present study still warrants controlled studies in humans.

Introduction

Epilepsy affects about 1% of world population, 30% of whom are pharmaco-resistant [1]. Surgical excision and/or disconnection of the epileptic focus are treatment options suitable for only few selected cases. Indeed, based on strict criteria for patient selection for epilepsy surgery about 20% of patients suffering from pharmaco-resistant epilepsy are candidates for surgical resection [2]. Those in whom resective surgery failed or is not possible require exploration of new modalities of treatment like deep brain

Abbreviations: AC-PC, anterior commissure–posterior commissure; ECoG, electro-corticogram; DBS, deep brain stimulation; GP, globus pallidus; GPe, external part of globus pallidus; GPi, internal part of globus pallidus; HFS, high frequency stimulation; SEM, standard error of the mean; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

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* Corresponding author. Institut des Neurosciences de Grenoble, INSERM U836 - Equipe 11, Bâtiment Edmond J Safra, BP 17038042 Grenoble Cedex 9, France. Tel.: +33 4 56 52 06 27; fax: +33 4 56 52 06 39.
E-mail address: brigitte.piallat@ujf-grenoble.fr (B. Piallat).

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stimulation (DBS). There are several potential targets investigated for DBS in epilepsy. These include amygdala and hippocampus [3,4] for mesial temporal lobe epilepsy, and mamillary body and mamillo-thalamic tract for unresectable lesional epilepsy in patients with hypothalamic hamartoma [5]. The cerebellum [6,7], the centro-median nucleus of thalamus [8] and the caudate nucleus [9] have also been tested in other forms of epilepsy. However, the efficacy of these targets has not been established beyond certainty as usually only few cases were reported and when existing, clinical trials have brought out variable results. Of particular interest, the large multicentric double blind trial of stimulation of the anterior nucleus of thalamus (SANTE) reported a promising two years follow up showing a median seizure reduction of 56% and 54% of patients had a reduction of 50% or more in their seizure frequency [10].

Motor epilepsies are particularly challenging when medications have failed. Seizures originating primarily from the motor strip can be tonic and can create clonic jerks of any part of the contralateral hemibody. They can produce falls and accidents due to motor impairment. In a clinical setting, frequent motor seizures also mean a restricted motor activity, a loss of independence in some cases and a need for supervision and monitoring by care givers. This may reflect negatively on quality of life. Because surgical resection of the motor strip can lead to a definitive partial or complete contralateral motor deficit, DBS of the motor part of basal ganglia could be an alternative strategy for the treatment of refractory motor epilepsy.

Some experimental data support the contribution of the motor part of basal ganglia nuclei in focal motor seizures. Deoxyglucose autoradiography studies showed the implication of putamen, globus pallidus (GP) and substantia nigra pars reticulata (SNr) in rat [11] and monkey [12–16]. Electrophysiological recordings have shown that neuronal activity of caudate nucleus, entopeduncular nucleus and SNr is modified by interictal spikes produced by penicillin injection in the neocortex of the cat [17] and rat [18]. In the alumina cream monkey model of motor focal seizure, 100 Hz electrical stimulation of the head of caudate nucleus could reduce the frequency of seizures [19]. However, internal GP (GPi) stimulation was found to cause reproducible maximum expression of electrographic and clinical seizure phenomena for the 90-s duration of the stimulus [16].

To clarify subcortical pathways of focal motor seizures, we recently recorded input basal ganglia structures in the penicillin monkey model [20]. Penicillin is a well-known proconvulsant agent [21], and when injected intracortically, it produces GABA blockade of cortical interneurons. Intracortical injection of penicillin in primary motor cortex produces subchronic, predictable, reproducible and pharmaco-resistant motor seizures [22]. The later feature has been also reported earlier in studies showing that penicillin-induced epileptiform foci in the rat appeared to be resistant to various anticonvulsant drugs [23,24]. In primate model, we have shown that the external part of globus pallidus (GPe) – subthalamic nucleus (STN) network was involved in motor seizures [20]. These data suggested that a disruption of activity in the STN and/or in the GPe could help in abolishing the expression of pathological excessive cortical synchronization during focal motor seizures. The exact mechanism through which HFS-STN produces results is open for debate. However it is likely that the effectiveness of DBS lies in the dissociation of input/output relationships of the stimulated nucleus, which disrupts information flow through the cortico-basal ganglia loops (for review see Ref. [25]). Operationally, the mechanism would alter the STN activity, thereby producing similar therapeutic effects to lesions or of silencing of this nucleus [26]. Taking together, all those data lead us to test the hypothesis that that HFS-STN could control focal motor seizures in a primate model of motor seizures induced by intracortical injection of penicillin. We used a non-human primate model for his close similarities with human cortex anatomical features and connectivity of basal ganglia, and also because motor seizures model in the primate was shown to be reproductible and shared similarities with motor seizures encountered in human [22]. Moreover, the non-human primate is also particularly pertinent in order to test DBS using the same devices commonly used in humans being.

Methods

Animals

This study was conducted on two monkeys (*Macaca fascicularis*): 1 female, 10 years old weighing 5 kg (A1) and 1 male, 7 years old weighing 11.4 kg (A2). They were individually housed in a temperature ($24 \pm 1^{\circ}$) and humidity ($50 \pm 5\%$) controlled facility with a 12 h light dark cycle (lights on 8:00 a.m.). Each monkey had free access to standard primate chow and water. In addition, fruits were given twice a day. The experiments were performed in accordance to the French guidelines on the use of living animals in scientific investigations with the approval of our local Ethical Committee for care of laboratory animals. All experimenters received proper training and certification for animal experimentation. Every effort was made to minimize animal's suffering while maximizing the data obtained.

Surgery

Surgery was performed under aseptic conditions and general anesthesia using ketamine hydrochloride (Imalgen®, Merial, Lyon, France) and xylazine (10 mg/kg and 1 mg/kg, im, respectively, loading dose) plus supplemental doses of both (5 mg/kg and 0.5 mg/kg, im, respectively, for maintenance). In addition, 1% lidocaine was used for local anesthesia of the scalp and muscles. Saline solution (NaCl 0.9%, Sigma-Aldrich, Lyon, France) was continuously infused intravenously during the operation for drug access and hydration. Surgery was performed with a stereotactic frame (David Kopf Instruments, Tujunga, California, USA) under intraoperative radiographic control. The prior coordinates of the STN were determined on an atlas of *M. fascicularis* brain [27] merged with an anatomical MRI and ventriculographic landmarks (midline, anterior and posterior commissures (AC-PC), height of the thalamus) using visual inspection of superimposed images in Photoshop software (Adobe Systems Inc., San Jose, CA). The STN was located at the following stereotactic coordinates: anterior 6/12th of the AC-PC line, lateral 5–6 mm, height: −1/8th of the height of the thalamus below AC-PC line [28,29]. A cannula was stereotactically placed in the right lateral ventricle through which 2 ml of ventricular contrast (Iopamiron 200, iodine 200 mg/ml, Bracc, Italy) was injected (Fig. 1A and B). In addition, a single sterile microelectrode (Tungsten microelectrode, impedance: 2–3 mega Ohm, FHC Inc, Bowdoin, USA) was used with specific software (LeadPoint3, Medtronic, USA) to confirm STN targeting in progressive descending plans in the vertical axis. The height of STN was clearly discernible from superior and inferior structures by its typical neuronal activity (dense and tonic). A definitive quadrielectrode lead (length 20 cm, 4 contacts numbered from 0 (the deeper) to 3, contact length 0.5 mm, outer diameter of electrode 0.74 mm spaced 0.5 mm apart, Numed, USA) was implanted so that at least 2 contacts out of the four were in the STN. The lead was anchored extra cranially to a screw and fixed with acrylic cement. In order to identify the motor region of the arm, we used epidural bipolar stimulation (1–5 mA, 5 Hz, DS8000, WPI, Stevenage, UK) delivered above the presumed motor cortex. One cannula was then inserted across the skull over the arm motor cortex territory for further penicillin injection on demand. Five stainless steel screws (G2 as