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Research Report

Deep brain stimulation of the substantia nigra pars reticulata exerts long lasting suppression of amygdala-kindled seizures

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ARTICLE INFO

Article history:
Accepted 16 March 2006
Available online 2 May 2006

Keywords:
Epilepsy
Rat
Basal ganglia
Intractable epilepsy
High frequency stimulation

ABSTRACT

Deep brain stimulation (DBS) has been used to treat a variety of neurological disorders including epilepsy. However, we have limited knowledge about effective target areas, optimal stimulation parameters, and long-term effect of DBS on epileptic seizures. Here we examined the effects of DBS of the substantia nigra pars reticulata (SNr) on amygdala-kindled seizures. Microwire electrodes were implanted into the SNr and amygdala of adult male rats. When stage 5-kindled seizures were achieved by daily amygdala kindling, high frequency stimulation was delivered to the SNr bilaterally 1 s after cessation of kindling. Our DBS protocol completely blocked kindled seizures in 10 out of 23 (43.5%) rats studied. Furthermore, when the same amygdala kindling procedure was performed 24 h later without DBS, the kindling failed to elicit any seizure signs in 6 of these 10 rats. Some of the post-DBS period of seizure suppression lasted for up to 4 days. In other 3 rats, only mild stage 1 to 2 seizures appeared following amygdala kindling. Only 1 of the 10 rats for which DBS had blocked kindled seizures exhibited full-scale 5 stage-kindled seizures 24 h after DBS. These results suggest that highly plastic neural networks are involved in amygdala-kindled seizures and that DBS, if well timed with the onset of amygdala kindling, may exert long lasting effects on the networks that may prevent the recurrence of kindled seizures.

1. Introduction

Epilepsy is a highly prevalent neurological disorder affecting 1–2% of the population. Although medication and surgical ablation treatments provide relief for 75% of patients with epilepsy, the condition is medically intractable for the remaining quarter of epileptic patients, approximately 10 million individuals (Litt and Lehnertz, 2002). For these intractable cases, deep brain stimulation (DBS) may offer hope for alleviation of this debilitating condition. Crucial questions are yet to be answered as to where are the best stimulation targets and what are the optimal stimulation protocols. To answer these questions, extensive basic and clinical researches need to be conducted in different type of epileptic seizures.

Electrical brain stimulation has been applied in the clinic to treat epilepsy for more than three decades (Chang, 2004). Cooper et al. (1973, 1976) initial approach was to apply stimulation to the cerebellum. In later work the stimulation targets were extended to include the anterior and central thalamic nuclei (Fisher et al., 1992; Lozano et al., 2000). Studies in animal models of epilepsy in the 1980s focused on the role of the basal ganglia in the regulation of epileptic seizures (Garant and Gale, 1983, 1987; McNamara et al.,

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doi:10.1016/j.brainres.2006.03.050

1984). Gale (1985) proposed a nigra control of epilepsy system in which the substantia nigra pars reticulata (SNr) inhibited the anticonvulsant zone in the ventral part of the superior colliculus. Gale's model was based on the findings that lesioning or pharmacological inhibition of the SNr could disinhibit the anticonvulsant zone and thus suppress epileptic seizures; conversely, SNr activation facilitated seizures. The view that nigral inhibition suppresses epileptic seizures has been reinforced by experiments showing that manipulation of structures upstream of the SNr, such as the striatum and subthalamic nucleus (STN), can also regulate seizure expression. For example, lesioning of the STN, the nucleus that sends excitatory glutamatergic projection to the SNr, reduced seizural responses to a chemical stimulus (Velisek et al., 2002; Veliskova et al., 1996; Dybdal and Gale, 2000).

DBS of basal ganglia structures, including the STN and SNr, has been explored as an epilepsy treatment strategy in both clinical settings and animal models. Velisek et al. (2002) reported that high frequency stimulation of the SNr could suppress seizures induced by chemical stimulation. In the present study, we tested whether DBS of the SNr could block amygdala-kindled seizures.

2. Results

Daily kindling induced progressive symptoms of seizures as characterized by Racine (1972), from stereotypic sniffing, jaw movement, facial clonus, rearing, and forelimb clonus to a stage 5 generalized clonic seizures, in which the rat fell. This progression to stage 5 seizures took a period of 1 to 2 weeks. When stage 5 seizures were consistently being evoked by amygdala kindling, the effects of high frequency stimulation of the SNr on kindled seizures were examined.

DBS of the SNr completely blocked amygdala-kindled seizures in 10 out of 23 rats (43.5%). The occurrence of kindled seizures in these 10 rats throughout the experimental sessions is depicted in Fig. 1. In these cases, the same intensity of amygdala kindling that had consistently induced stage 5 clonic motor seizures without DBS did not induce any noticeable signs of seizures when followed by DBS. The animals behaved normally during the 20-s period of DBS and thereafter. In most cases, the effects of DBS lasted more than 24 h. In the session 24 h after the initial successful DBS session, the same amygdala kindling, in the absence of DBS, did not induce full scale, stage 5-kindled seizures in 9 out of 10 cases (90% of cases). In 6 cases (60%), no seizure signs were observed following amygdala kindling in the session 24 h after DBS. In 3 cases (30%), mild stage 1–2 seizure signs (jaw movement, nodding of the head) were observed, and only 1 rat (10%) manifested full scale, stage 5 seizures as a result of amygdala kindling 24 h after the DBS session.

The duration of the seizure suppressive effects of DBS differed among rats. In 6 rats (60%) in which DBS immediately blocked seizures, only one subsequent seizure-free or seizure-attenuated session occurred following the DBS session. Three of the rats that had successfully been treated with DBS (30%) experienced more than one subsequent kindling session in the absence of DBS without full scale, stage five seizures: 1 rat had 2, 1 rat had 3, and 1 rat had 4 seizure-free or seizure-attenuated sessions (10% each). When seizures finally did resume in the case with 4 seizure-free sessions post-DBS, the seizural behaviors were markedly different from the original seizures observed before DBS in that the onset of seizures was much slower and milder. Originally, the rat experienced seizures in which rearing and severe forelimb clonus took place immediately following kindling stimulation (< 2 s). The kindled seizures that developed 4 sessions following DBS were characterized by an onset of rearing that took place 35 s following kindling stimulation and the forelimb clonus was much milder than the original kindled seizures observed before DBS.

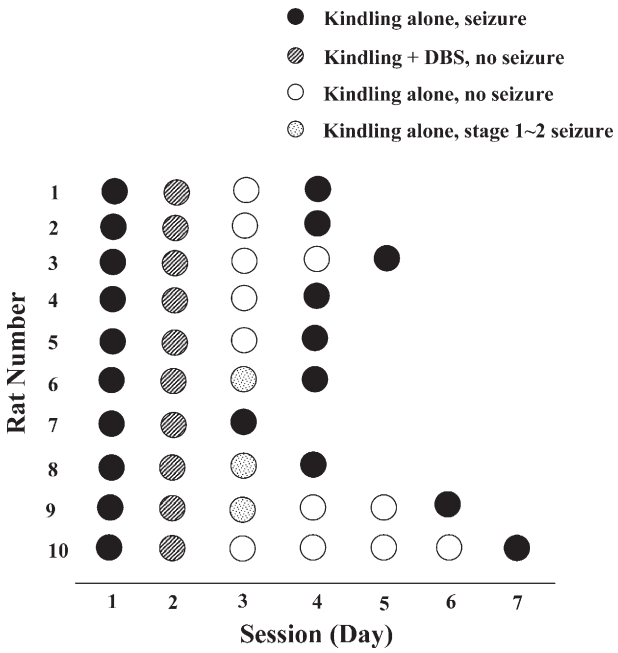

Fig. 1 – DBS of the SNr suppresses amygdala-kindled seizures. Bilateral high frequency stimulation of the SNr completely blocked amygdala-kindled seizures in 10 rats. In the following kindling session without DBS (session 3), all but one of these 10 rats did not exhibit clonic motor seizures. Among them, 6 rats did not have any seizure signs and 3 rats exhibited mild stage 1–2 seizures. The experimental session numbers are showed on the abscissa and the rats' numbers are listed on the ordinate.

Fig. 2 summarizes the effect of DBS of the SNr on amygdala-kindled seizures. Complete blockade of kindled seizures took place in the session with DBS of the SNr. A significant decrease in seizure occurrence was observed in sessions following the DBS sessions ($P < 0.001$ Chi-square test). Reduced seizure occurrence was found in the second sessions following DBS; however, the difference failed to reach statistically significant level ($P = 0.06$).

The loci of the SNr DBS sites were determined by postmortem histological examination and are depicted in Fig. 3. Note that most of the effective stimulation electrodes were located in the anterior part of the SNr. Meanwhile in most of the cases where the DBS did not have an effect on

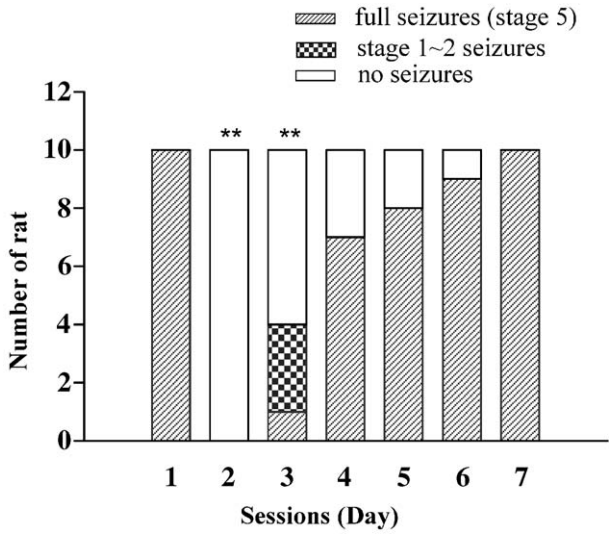

Fig. 2 – The effect of DBS of the SNr on amygdala-kindled seizures. The number of rats exhibiting different stages of seizures was compared between control (the session before DBS) and during/after DBS sessions. A significant decrease in seizure occurrence was detected in the sessions during and immediately following DBS ($P < 0.001$, Chi-square test).**

kindled seizures, the electrodes were located either outside of the SNr or in the posterior part of the SNr.

3. Discussion

Amygdala kindling can rewire the brain network and induce clonic motor seizures evolved through 5 different stages (Racine, 1972). Instead of uniformly activated whole brain homogeneously, a network subserving amygdala-kindled seizures involves brain regions pathologically connected by repeated kindling stimulation (Morimoto et al., 2004; Blumenfeld, 2005). Such emergent properties of neural network that subserve the ability of the brain to undergo rapid global state changes, can be the target of anticonvulsant drugs (Faingold, 1999, 2004). By the same token, deep brain stimulation can modify the emergent property by hitting pivotal structures necessary for propagation of ictal discharges during amygdala-kindled seizures.

One of the candidates for such a pivotal structure is the basal ganglia. Most studies examining the role of the basal ganglia in epilepsy have focused on the SNr, the output nucleus of basal ganglia where the direct and indirect pathways converge (Alexander et al., 1990). Several lines of evidence have indicated that the SNr is critically involved in epileptic seizures: (1) Microinjection of GABA or other GABA receptor agonists into the SNr blocks seizures induced by chemical stimulation (Iadarola and Gale, 1981; Zhang et al., 1989), kindling (Loscher et al., 1987; McNamara et al., 1984; Deransart et al., 1998a), electroshock (Mirski et al., 1986), audiogenic stimulation (Gonzalez and Hettinger, 1984), and genetic manipulations (Deransart et al., 1998b). (2) Lesions of SNr appear to suppress kindling (McNamara et al., 1984; Shin et al., 1987), bicuculline- and electroshock-induced seizures (Garant and Gale, 1983). (3) Electrical stimulation of the SNr within a wide range of frequencies (from 3 to 130 Hz) attenuates cortical epileptiform activity (Boda and Szente, 1992; Sabatino et al., 1988) and blocks flurothyl- and kindling-induced seizures (Morimoto and Goddard, 1987; Velisek et al., 2002). All of these results suggest that inhibition of SNr's GABAergic inhibitory outputs can suppress seizures.

Other basal ganglia structures, either directly or indirectly connected to the SNr, may also be involved in modulation of seizures. Microinjection of GABA receptor antagonists into the striatum has been shown to protect against amygdala-kindled and bicuculline-induced seizures in the rat, perhaps via an afferent inhibition of the direct pathway (Cavalheiro et al., 1987; Turski et al., 1989). Likewise, local injection of GABA receptor agonists in the STN significantly reduces motor seizures (Deransart et al., 1998a; Veliskova et al., 1996). This STN inhibition could be mediated by a decrease in excitatory input to the SNr via the indirect pathway. Based on such experimental data indicating that modulation of the SNr circuit can suppress epileptic seizures, DBS of basal ganglia regions has been tested in both experimental animals and epileptic patients. Recent clinical trials have tested the effects of DBS of the STN on epileptic seizures (Benabid et al., 2000; Bingaman et al., 2000; Chabardes et al., 2002). In animal experiments, DBS of both the SNr (Morimoto and Goddard, 1987; Velisek

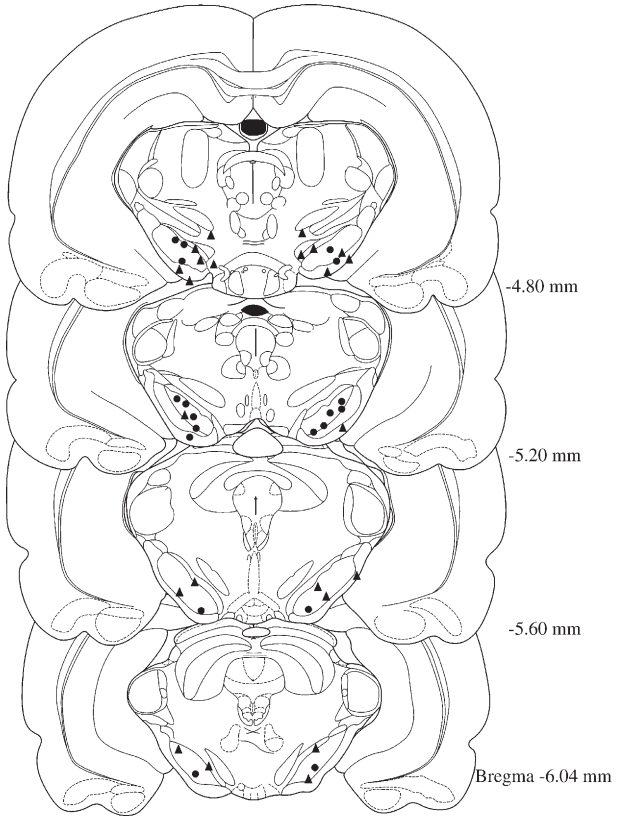

Fig. 3 – Loci of stimulation electrodes aimed at the SNr.
● = electrodes that blocked amygdala-kindled seizures.
▲ = Electrodes that did not affect amygdala-kindled seizures.

et al., 2002) and STN (Hashizume et al., 2004; Usui et al., 2005; Vercueil et al., 1998) has been observed to suppress different epileptic seizures.

It is reasonable to suppose that DBS exerts inhibitory effects on seizure activity via actions on the SNr neurons, since this local inhibition theory is widely accepted as the mechanism underlying the therapeutic effects of subthalamic DBS on Parkinson's disease. However, there is no direct evidence supporting this local inhibition theory. Indeed the opposite response, local excitation, may take place as high-frequency stimulation drives local neurons into high-frequency firing. This certainly can happen in the STN and SNr, since both are known to have high baseline firing rates (Garcia et al., 2003; Kitai and Kita, 1987). Furthermore, unlike the narrow range of effective frequency of STN stimulation in Parkinson's disease, the effective frequency range for SNr stimulation in epilepsy treatment is quite broad (3 to 130 Hz). It is unlikely that such disparity in frequency would consistently generate similar inhibitory responses. Furthermore, DBS could totally block kindled seizures in our experiments, while pharmacological inhibition of SNr only suppressed motor components of kindled seizures (Deransart et al., 1998a; Loscher et al., 1987). Moreover, the seizure suppressive effects of DBS in our experiment lasted longer than pharmacological inhibition of the SNr. These results indicate that inhibition of the SNr cannot solely account for the mechanisms underlying DBS.

Since epileptiform discharge is characterized by hypersynchronized action potentials, DBS may disrupt synchronization, rather than provide inhibition. Evidently, this stimulation needs to be applied to a pivotal structure in the network that gates the propagation of epileptiform activities. Our previous electrophysiological work revealed that SNr neurons led STN and hippocampus neurons in synchronized firing during amygdala-kindled seizures (Woodward et al., 2003), reinforcing the view that the SNr mediates a crucial role in amygdala-kindled seizures.

In summary, the present study demonstrates a long lasting antiepileptogenesis effect of high frequency stimulation of the SNr on amygdala-kindled seizures. To block amygdala-kindled seizures, the stimulation needs to be delivered in the pivotal structure at vulnerable phases of oscillatory network (Tass, 2000, 2003). Neurochemical and electrophysiological mechanisms underlying such long lasting antiepileptogenesis effect merit further studies. Information obtained from these studies may help us to design clinical treatment of patients with intractable epilepsy.

4. Experimental procedures

Twenty-three male Sprague–Dawley rats weighing 350–400 g (around 3–4 months old) were used in the experiment. Animals were housed individually under a reversed dark–light cycle (lights off from 7:00 to 19:00) for 7 days before surgery. Animals were treated in accordance with the U.S. Public Health Service *Guide for the Care and Use of Laboratory Animals*. The experiments were approved by the Institute Animal Care and Use Committee of Wake Forest University School of Medicine.

4.1. *Surgery procedures*

Rats were anesthetized with ketamine (100 mg/kg, i.m.) and xylazine (10 mg/kg, i.m.). An array of eight platinum-iridium Teflon-insulated microwires (50 μm diameter, Biographic Inc. Winston-Salem, NC), soldered to connecting pins on a headstage, were stereotaxically lowered bilaterally into the SNr (5.3 mm posterior to the Bregma (A), 2.3 mm lateral (L) to the midline, and 7.8 mm ventral (V) to the dura) and into the basolateral amygdala (1.0 mm A, 3.2 mm L, and 6.0 mm V). The headstage was secured onto the cranium with dental acrylic cement and anchoring screws. Animals were housed individually and allowed to recover from surgery for at least 14 days before commencement of the kindling experiment.

4.2. *Behavioral tests*

Kindling stimulation was delivered daily into one side of the amygdala (1 s stimulation train at 60 Hz, 1 ms pulse width, 100–300 μA). The stimulation was delivered when the rat was at rest, usually 10 min into the experimental session. Animal behavior was recorded with a video camera (30-ms resolution) and analyzed to identify different stages of kindled seizures. Five stages of seizures were developed during the kindling process over a period of 1–2 weeks. Stage 1 seizures started with immobility, eye closure, and stereotypic sniffing. In stage 2 seizures, facial clonus (chewing) and head nodding occurred. Stage 3 seizures were characterized by a unilateral forelimb clonus (contralateral to focus) followed by stage 4 seizures in which a rearing and bilateral forelimb clonus took place. In final stage 5 seizures, the rat expressed vigorous rearing, forelimb clonus, and falling.

The DBS experiment was conducted after stage 5-kindled seizures were constantly expressed over at least 3 sessions. The intensity of DBS was tested first in the session. The intra-SNr stimulation current was adjusted so that no signs of side effects (turning, rearing, facial, and limb muscle contraction) were observed for at least 5 min before administration of the experimental DBS protocol. Twenty second DBS (130 Hz, 60 μs pulse width, and 100–200 μA) was delivered bilaterally to the SNr 1 s after cessation of the kindling stimulation. The behaviors of rats were analyzed in DBS sessions to determine the effects of DBS on kindled seizures. In the case where the DBS blocked kindled seizures, kindling stimulation with identical parameters as that used in control and DBS sessions were delivered in the next session 24 h later and the behavioral responses to the DBS were analyzed. If seizures were absent or substantially attenuated in such a session, identical kindling procedure was continued until the stage 5 seizures appeared again. To control for the malfunction of stimulation device, rats at different stage of experiments were tested in the same day so at least one rat would exhibit 5 stage-kindled seizures in each day of experiment.

4.3. *Histological localization of stimulation sites*

At the conclusion of the final experimental session, each animal was subjected to the same anesthesia as in surgery. A positive current of 10–20 μA was passed through selected microwires for 10–20 s to deposit iron ions, animals were then

sacrificed and perfused intra-cardially with 4% paraformaldehyde solution. Coronal sections (45 μm thick) were cut through the SNr and amygdala and mounted on slides. For the platinum iridium microwires, electrode tips were visualized as a lesion spot with neutral red staining. Boundaries of the four brain areas were assessed with reference to the rat brain atlas of Paxinos and Watson (1986).

4.4. *Data analysis*

The behavior outcome of the rats after kindling stimulation was scored according to the symptoms of seizures as characterized by Racine (1972). The effect of DBS on kindled seizure was measured by non-parametric Chi-square test. The number of rats with different degree of seizures in each session was counted and compared with the control session before DBS. Comparisons that differed with $P < 0.05$ were considered significant in all conditions.

Acknowledgments

This study was supported by NIH grants NS-43441 and NS 40628, TW-006144 to JYC and NS-19608 to DJW, National Natural Science Foundation of China (30170307, 30370461) to FL.

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