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Ventral pallidum deep brain stimulation attenuates acute partial, generalized and tonic-clonic seizures in two rat models

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ABSTRACT

Approximately 30% of individuals with epilepsy are refractory to antiepileptic drugs and currently approved neuromodulatory approaches fall short of providing seizure freedom for many individuals with limited utility for generalized seizures. Here, we expand on previous findings and investigate whether ventral pallidum deep brain stimulation (VP-DBS) can be efficacious for various acute seizure phenotypes. For rats administered pilocarpine, we found that VP-DBS (50 Hz) decreased generalized stage 4/5 seizure median frequency from 9 to 6 and total duration from 1667 to 264 s even after generalized seizures emerged. The transition to brainstem seizures was prevented in almost all animals. VP-DBS immediately after rats exhibited their first partial forebrain stage 3 seizure did not affect the frequency of partial seizures but reduced median partial seizure duration from 271 to 54 s. Stimulation after partial seizures also reduced the occurrence and duration of secondarily generalized stage 4/5 seizures. VP-DBS prior to pilocarpine administration prevented the appearance of partial seizures in almost all animals. Lastly, VP-DBS delayed the onset of generalized tonic-clonic seizures (GTCSs) from 111 to 823 s in rats administered another chemoconvulsant, pentylenetetrazol (PTZ, 90 mg/kg). In this particular rat seizure model, stimulating electrodes placed more laterally in both VP hemispheres and more posterior in the left VP hemisphere provided greatest efficacy for GTCSs. In conclusion, our findings posit that VP-DBS can serve as an effective novel neuromodulatory approach for a variety of acute seizure phenotypes.

1. Introduction

Pharmacotherapy is the primary treatment option for 65 million people worldwide with epilepsy (Ngugi et al., 2010; Thurman et al., 2011). However, approximately one third are refractory to this approach (Kwan and Brodie, 2006) and require other approaches. In the United States, 750,000 people are refractory to pharmacotherapy and 200,000 of them may be candidates for resective surgery. However, only 1500–3000 undergo surgery each year due to low candidacy and referral rates (Engel, 1996; Engel et al., 2003; Jobst and Cascino, 2015) and ~35% still have recurrent seizures despite resection (Ramesha et al., 2011; Spencer et al., 2005; Tellez-Zenteno et al., 2005). Moreover, resection is particularly effective for individuals with temporal lobe epilepsy (Spencer et al., 2005; Wiebe et al., 2001), but less so for those with seizures that originate in frontal, parietal, or occipital areas or those who have generalized seizures (DeGiorgio and Krahl, 2013; Wiebe et al., 2001). Therefore, until pharmacotherapy or resective outcomes and numbers improve, a considerable number of people remain untreatable and an alternative approach is urgently needed. Neuromodulation, and in particular deep brain stimulation (DBS), may achieve this goal. Vagus nerve stimulation (VNS) (DeGiorgio and Krahl, 2013) and responsive neurostimulation (RNS) (Morrell, 2011) are the only FDA-approved neuromodulatory approaches for epilepsy in the United States. The former involves the electrical stimulation of the vagus cranial nerve (Rajna and Lona, 1989) and results in a responder rate of 43% (DeGiorgio and Krahl, 2013; DeGiorgio et al., 2000; Handforth et al., 1998; Morris and Mueller, 1999) with efficacy more towards frontal onset partial seizures (Burakgazi et al., 2011). The latter is a closed-loop system that delivers electrical stimulation at the seizure foci once epileptiform activity is detected (Morrell, 2011; Skarpaas and Morrell, 2009) and can reduce seizures by 66% (Bergey et al., 2015; Morrell and Halpern, 2016). However, no seizure-freedom was noted

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lasting the entire 6 year period with RNS (Bergey et al., 2015; Morrell and Halpern, 2016) and its efficacy favors partial temporal and neocortical onset seizures (Browning et al., 1989; Morrell, 2011; Skarpaas and Morrell, 2009). Taken together, VNS and RNS are effective treatment options for individuals with intractable epilepsies, but limitations in efficacy warrant the investigation for other neuromodulatory approaches.

Recently, we reported that deep brain stimulation of the ventral pallidum (VP-DBS), a basal ganglia structure, prevented secondarily generalized forebrain and brainstem seizures in the pilocarpine rat model of temporal lobe epilepsy (TLE) when applied prior to chemoconvulsant administration. Notably, VP-DBS did not affect motor function in non-seizing rats in the open field test. (Yu et al., 2016). We chose to electrically stimulate the VP since epileptiform activity was shown to appear in this brain area prior to the hippocampus (Clifford et al., 1987) suggesting that the VP may be an upstream epileptogenic foci. Further, pharmacological activation of VP neuronal activity attenuated generalized seizures in the absence rat model of epilepsy and this brain area has extensive connections to limbic, basal ganglia, midbrain and brainstem structures (Groenewegen et al., 1993; Haber et al., 1993) that may provide multiple neural substrates for VP GABAergic modulation.

Although our findings revealed a novel potential for anticonvulsant efficacy with VP-DBS when turned on before chemoconvulsant administration, we did not investigate whether the timing of VP-DBS would limit the scope, utility and efficacy for VP-DBS to attenuate various acute seizure phenotypes in pilocarpine-treated animals or examine whether VP-DBS could be efficacious in another rodent seizure model. With that in mind, we examine in this study whether VP-DBS is efficacious for partial and generalized seizure phenotypes even after these seizures have already emerged. Lastly, we test whether VP-DBS can affect generalized tonic-clonic seizures (GTCSs) in a high-dose pentylenetetrazol (PTZ) rat model to validate the scope and potential for VP-DBS efficacy for other seizure phenotypes using another rat model of seizures.

2. Materials and methods

2.1. Animals and craniotomy surgeries

Animal use was conducted in accordance with the Albany Medical College institutional animal care and use committee consistent with the National Institutes of Health guidelines for the care and use of laboratory animals. All experiments were completed during the light phase of the light-dark cycle, from 7:00 AM–7:00 PM. We used male Sprague Dawley rats weighing 170–240 g, which were purchased from Taconic (Germantown, NY) or Charles River Laboratories (Kingston, NY).

To implant stimulating and recording electrodes, animals were anesthetized using 2% isoflurane in an inhalant system (Harvard Apparatus, MA, USA) and craniotomy surgeries were performed using a stereotactic frame (David Kopf Instruments, CA, USA). Animal body temperature was maintained between 36 and 37 °C using a homeothermic monitoring system (Harvard Apparatus, MA, USA). According to identified brain coordinates, burr holes were drilled in the skull and stainless steel twisted wire electrodes (125 μm per wire, Plastics One, VA, USA) for bipolar electrical stimulation were implanted bilaterally in the VP (from bregma: 0.3 mm posterior, 2.2 mm laterally, and 7.2 mm ventral from the dura). Along with stimulating electrodes, a screw electrode was implanted in the right primary somatosensory cortex (S1) (from bregma: 4.3 mm posterior, 3.6 mm laterally) to monitor electrocorticograms (eCoGs). Two anchor screws were placed in the front two quadrants of the skull to give stability to the dental cement cap. Electrodes, anchor screws, and a plastic pedestal were fastened to the skull using dental cement (Duralay Reliance Dental, IL, USA). Post-operative care included the administration of penicillin subcutaneously (subQ) (80 μg/kg) immediately following surgery and buprenorphine HCl (0.3 mg/mL) subQ twice daily for 2 days following surgery for pain.

2.2. Animal seizure models and behavioral testing

All animal behavioral testing was performed at least one week post-craniotomy surgery. To evaluate the breadth of VP-DBS efficacy and lend stronger scientific rigor that this neuromodulatory approach can attenuate seizing behavior, we tested this in two different rat acute seizure models: the pilocarpine rat model of temporal lobe epilepsy (TLE) and a high-dose pentylenetetrazol (PTZ) rat model for GTCSs. For the former, we administered 1 mg/kg of scopolamine subcutaneously 30 min prior to an intraperitoneal (IP) injection of 400 mg/kg pilocarpine. For the latter group, we IP injected 90 mg/kg to specifically elicit more severe GTCSs rather than the facial and forelimb clonus that are induced at lower PTZ concentrations (Hosseini et al., 2009; Loscher et al., 1991; Nassiri-Asl et al., 2008).

In rodents, forebrain and brainstem seizures are two largely independent seizure systems in the brain. Forebrain seizures have a lower threshold for seizure induction than brainstem seizures (Applegate et al., 1991; Browning et al., 1993; Magistris et al., 1988) with facial and forelimb clonus in the former (Racine, 1972b) and tonic extensions and clonic convulsive seizures with wild-running and jumping in the latter (Browning et al., 1993; Faingold, 1999; Gale, 1992). We characterize these as different seizure stages using the Racine scale (Racine, 1972a,b) modified to include brainstem seizure phenotypes as others did (Luttjohann et al., 2009; Stewart et al., 2001). Behavioral seizures were recorded and videos were analyzed by 1 un-blinded (EM) and 2 blinded reviewers (AZ, MR) using a Racine scale as follows; 1: staring and mouth clonus; 2: head nodding; 3: unilateral forelimb clonus; 4: rearing and bilateral forelimb clonus; 5: rearing and falling; 6: wild-running and jumping, 7: wild running and jumping followed by tonic-clonic extensions. For readability and simplicity, we denoted stages 1–3 as partial forebrain seizures; stages 4/5 as generalized forebrain seizures and stages 6/7 seizures as generalized brainstem seizures. We classified a behavioral seizure event if the aforementioned behavior lasted at least 5 s and a separate behavioral seizure event if it occurred more than 2 s after onset of non-seizing activity (Bergstrom et al., 2013; Yu et al., 2016); otherwise, we would view the two events as a prolonged single behavioral seizure.

For the PTZ seizure model, the latency to GTCSs was determined from recorded videos with time 0 s denoted as the time of PTZ administration. A GTCS event was characterized by bilateral forelimb tonic extension with hind leg kicking preceded by myoclonic jerks and wild running lasting more than 5 s.

2.3. Stimulation and electrophysiological recordings

In the pilocarpine experiments, implanted rats were divided into two groups. The control group was comprised of animals administered pilocarpine without VP-DBS, which progressed through the different seizure phenotypes. In the experimental group, VP-DBS was turned on 1 h prior to pilocarpine and continuously throughout the monitored period in some experiments. In other experiments, VP-DBS was turned on when different stages of seizure phenotypes first emerged, which was dependent on the specific experiment with VP-DBS turned on for 1 h following the first stage 4/5 seizures and turned on for 30 min following the first stage 3 seizure. The VP-DBS duration was shorter in the stage 3 experiments to time-match un-stimulated animals since we noted in our previous study that it took a maximum of 30 min for animals to transition to stage 4/5 seizures (Yu et al., 2016). VP-DBS electrical stimulation was administered at 50 Hz, 300 μA, 90 μsec duration in the cathodal bipolar configuration using a Grass S88X dual stimulator (Natus Neurology Inc, RI, USA) coupled to two current isolation units (Natus Neurology Inc, RI, USA) and a HumBug 50/60 Hz noise eliminator (Quest Scientific, Van, Canada). In our previous study,