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Research report

Acute deep brain stimulation in the thalamic reticular nucleus protects against acute stress and modulates initial events of adult hippocampal neurogenesis

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HIGHLIGHTS

- Acute deep brain stimulation in the TRN protects against acute stress.
- Acute deep brain stimulation in the TRN increases cell proliferation in the hippocampus.
- TRN might be a potential target for DBS to treat mood disorders.

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ABSTRACT

Deep brain stimulation (DBS) is used as an alternative therapeutic procedure for pharmacoresistant psychiatric disorders. Recently the thalamic reticular nucleus (TRN) gained attention due to the description of a novel pathway from the amygdala to this nucleus suggesting that may be differentially disrupted in mood disorders. The limbic system is implicated in the regulation of these disorders that are accompanied by neuroplastic changes. The hippocampus is highly plastic and shows the generation of new neurons, process affected by stress but positively regulated by antidepressant drugs. We explored the impact of applying acute DBS to the TRN (DBS-TRN) in male Wistar rats exposed to acute stress caused by the forced-swim Porsolt's test (FST) and on initial events of hippocampal neurogenesis. After the first session of forced-swim, rats were randomly subdivided in a DBS-TRN and a Sham group. Stimulated rats received 10 min of DBS, thus the depressant-like behavior reflected as immobility was evaluated in the second session of forced-swim. Locomotricity was evaluated in the open field test. Cell proliferation and doublecortin-associated cells were quantified in the hippocampus of other cohorts of rats. No effects of electrode implantation were found in locomotricity. Acute DBS-TRN reduced immobility in comparison to the Sham group ($p < 0.001$). DBS-TRN increased cell proliferation (Ki67 or BrdU-positive cells; $p = 0.02$, $p = 0.02$) and the number of doublecortin-cells compared to the Sham group ($p < 0.02$). Similar effects were found in rats previously exposed to the first session of forced-swim. Our data could suggest that TRN brain region may be a promising target for DBS to treat intractable depression.

1. Introduction

Stress is considered a response for homeostasis preservation and survival [1]. Also, stress is one of the most important factors underlying affective disorders such as depression [2,3]. Depression is a neuropsychiatric disorder that courses with neurochemical,

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morphological, and behavioral alterations. It has been found that changes in neurocircuitry may be responsible for the manifestation of symptoms in mood disorders [4]. Neurocircuitry can be divided into 3 compartments: dorsal, ventral, and modulatory. Specifically, the dorsal compartment includes the thalamus, prefrontal cortices, premotor cortex, dorsal cingulate cortex, dorsal striatum, and the dorsal pallidum. Interestingly, several of these structures, such as the ventromedial prefrontal cortex, cingulate cortex, and nucleus accumbens (NAcb), have become beneficial targets for deep brain stimulation (DBS) to counteract depressive-like behavior in preclinical models, which suggests that this technique may have promising clinical application [4–6].

DBS delivers electrical stimulation to the brain through electrodes implanted in target areas. DBS has become a noteworthy alternative strategy for treating several neuropsychiatric disorders [7]. Currently, DBS is an attractive therapeutic alternative for treating pharmacotherapy-refractory major depression [4,8]. Preclinical studies have investigated the effects of using DBS on various brain targets, and the stimulation parameters have been adjusted according to the depressive-like experimental protocol [5].

DBS of the inferior thalamic peduncle and the thalamic reticular nucleus (TRN) may be effective at alleviating depression symptoms. These structures induce electrocortical synchronization and aid the inhibition of input of irrelevant stimuli [9,10]. Previous experiments from our group have found that DBS applied to the TRN in the rat can also induce antiepileptogenic effect [11]. The TRN occupies a key position relative to the thalamocortical (TC) and corticothalamic loops and is involved in the generation of sleep spindles and spike-wave discharges [12]. The TRN plays a critical role in thalamocortical (TC) dysrhythmia [13], which may be responsible for several neurological disorders. In this line, the TRN may be related to anxiety and perseveration behaviors [14,15]. Recently, study into a novel pathway that is involved in attentional and emotional processes found that the amygdala can send inputs to inhibit the TRN in monkeys, which could suggest that distinct mechanisms of attention to external and internal stimuli may be differentially disrupted in the mood disorders [16].

Regarding the alterations presented in mood disorders, many preclinical and few postmortem studies in humans have focused on the regulation of neurogenesis because antidepressant and antiepileptic treatments promote the generation of new neurons in the hippocampus [17]. In this sense, hippocampal neurogenesis is increased after stimulation of vagus nerve and after the DBS of the anterior thalamic nucleus [18,19]. Moreover, the stimulation of limbic targets promotes hippocampal neurogenesis in adult mice [20].

The rostral part of the TRN is connected to the motor and limbic centers, and the hippocampal formation accesses the rostral sector of the TRN [21]. This anatomical pathway may be enough to promote both behavioral changes and neuroplastic alterations by DBS to the TRN. Therefore, in this study, we evaluated the immobility behavior and EEG changes in freely moving rats after DBS-TRN. Additionally, we compared the effects of unilateral versus bilateral DBS-TRN on depressive-like behavior. Finally, we analyzed the effects of acute DBS-TRN on the early events involved in hippocampal neurogenesis in male Wistar rats.

2. Materials and methods

2.1. Animals

Male Wistar rats (280–320 g) were used in this study. Animals were housed in standard laboratory cages under 12-h light/dark cycles at a temperature of 23–25 °C with access to food and water *ad libitum*. Experiments were performed in accordance with the technical guidelines for the production, care and use of laboratory animals issued by SAGARPA (NOM-062 ZOO-1999), and the ethics committee of the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz approved all procedures. All efforts were made to minimize the suffering and number of animals used.

2.2. Surgical procedure and post-surgery recovery

Surgery was performed following intramuscular (i.m.) administration of ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (5 mg/kg). Stainless steel tripolar electrodes (0.300 mm diameter) were implanted in both the left and right TRN –two tips were used to stimulate and one tip was used to electroencephalographic recordings (EEG)- using the following coordinates [22]: AP, −1.4 mm; L, +1.7 mm; +H, 6.0 mm (Fig. 1). Epidural jewelry screws were implanted in the motor cortices (MCx) for EEG. The electrodes were welded into a mini-connector and fixed to the skull with dental acrylic. After surgery, the animals were treated with an analgesic (Butorphanol, 0.4 mg/kg) and an antibiotic (Amoxicillin, 0.6 mg/kg). Thereafter, the animals were individually housed in cages (50 × 27 × 30 cm) and were allowed to recover for 14 days.

2.3. Electrical stimulation and recording

Electrical stimulation was delivered to the animals using a Grass Instruments S88 stimulator (Grass, Quincy, MA, USA); a device enables automatic firing of the stimulator [23]. The stimulation parameters consisted of a 10-min sequence of biphasic square wave pulses at the following levels: frequency, 100 Hz; pulse width, 0.5 ms; and intensity, 200 μA. The recordings of the brain electrical activity were collected using polygraphic equipment model 78-E (Grass, Massachusetts).

2.4. Immunohistochemistry

The animals were sacrificed using an overdose of anesthetic and perfused with a 4% *para*formaldehyde solution (pH 7.4). Their brains were removed and maintained in the *para*formaldehyde solution for an additional 24 h. The fixed brains were then immersed in 30% sucrose and sliced using a platform-sliding microtome (Leica, Buffalo Grove, IL, USA) to obtain serial coronal sections (50 μm) from the dorsal to the ventral hippocampus. The sections were stored in a cryoprotective solution containing 25% ethylene glycol and 25% glycerol in 0.05 M phosphate buffer.

The sections were stained using the free-floating immunohistochemistry method, as previously described [24]. Prior to labeling the cellular populations involved in neurogenesis, we stained the serial sections using the Nissl method to visualize the position of the right electrode [25]. Only the coronal sections that were obtained from rats that had correctly implanted electrodes were used (~90%).

Thereafter, the tissue sections that were to be used for bromodeoxyuridine (BrdU), chlorodeoxyuridine (CldU) or iododeoxyuridine (IdU) immunodetection were pretreated with 2 N HCl at 37 °C for 15 min, followed by borate buffer neutralization. The brain sections that were to be used for the detection of Ki67, protein that is expressed in different phases of the cell cycle, and doublecortin (DCX) were pretreated with citrate buffer (pH 6.0) [24]. The tissue sections were incubated overnight with the following primary antibodies: rabbit anti-Ki67 (1:2000; Abcam, San Francisco, CA, USA), mouse monoclonal anti-BrdU (1:1000; BD, Franklin Lakes, NJ, USA) and goat anti-DCX (1:1000; Santa Cruz Biotech, Santa Cruz, CA, USA). The coronal tissue sections were extensively washed the next day, and biotinylated secondary antibodies were