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Behavioral, neurochemical and molecular changes after acute deep brain stimulation of the infralimbic prefrontal cortex

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ABSTRACT

Deep brain stimulation (DBS) is a treatment that has shown some efficacy in treatment-resistant depression. In particular, DBS of the subcallosal cingulate gyrus (Brodmann's area 25, Cg25) has been successfully applied to treat refractory depression. In the rat, we have demonstrated that DBS applied to infralimbic (IL) cortex elevates the levels of glutamate and monoamines in the prefrontal cortex, and requires the stimulation of cortical α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors for its antidepressant-like effects. However, the molecular targets of IL DBS are not fully known. To gain insight into these pathways, we have investigated whether IL DBS is able to reverse the behavioral, biochemical and molecular changes exhibited by the olfactory bulbectomized (OBX) rat. Our results revealed that 1 h IL DBS diminished hyperlocomotion, hyperemotionality and anhedonia, and increased social interaction shown by the OBX rats. Further, IL DBS increased prefrontal efflux of glutamate and serotonin in both sham-operated and OBX rats. With regard to molecular targets, IL DBS increases the synthesis of brain-derived neurotrophic factor (BDNF) and the GluA1 AMPA receptor subunit, and stimulates the Akt/mammalian target of rapamycin (mTOR) as well as the AMPA receptor/c-AMP response element binding (CREB) pathways. Temsirolimus, a known *in vivo* mTOR blocker, suppressed the antidepressant-like effect of IL DBS in naïve rats in the forced swim test, thus demonstrating for the first time that mTOR signaling is required for the antidepressant-like effects of IL DBS, which is in line with the antidepressant response of other rapid-acting antidepressant drugs.

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1. Introduction

Although the application of chronic stimulation of brain structures started with psychiatric patients as early as 1947 (see Hariz et al., 2010; for review), it was not until 2007 that deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) was approved by the US Food and Drug Administration for the treatment of refractory obsessive-compulsive disorders (Greenberg et al., 2010). Modern DBS is a routine therapy in several neurological disorders such as tremors, Parkinson's disease, dystonia and epilepsy (Krack et al., 2010). However, for the great majority of severe neuropsychiatric conditions, DBS is still under investigational development. Although early small-scale, open-label trials showed promise for DBS of the subcallosal cingulate gyrus (Brodmann's area 25, Cg25) or VC/VS to treat refractory depression (Mayberg et al., 2005; Malone et al., 2009; Holtzheimer and Mayberg, 2010; Kennedy et al., 2011; Puigdemont et al., 2012), recent studies have not proved efficacy in depression (Dougherty et al., 2015; see Morishita et al., 2014 for review, see also Crowell et al., 2015). In addition, both preclinical and clinical findings suggest that the use of anti-inflammatory drugs may attenuate the antidepressant response of DBS (Warner-Schmidt et al., 2011; Perez-Caballero et al., 2014), which argues in favor of an surgical, insertional effect rather than a stimulatory effect.

Nevertheless, several preclinical studies have shown antidepressant-like effects of DBS of the ventromedial prefrontal cortex (vmPFC), particularly the infralimbic prefrontal cortex (IL), which is considered to be the rodent homologous area of Cg25

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(Gabbott et al., 2003; Gass and Chandler, 2013). These effects are shown not only in naïve rats (Hamani et al., 2010; Lim et al., 2015; Etiévant et al., 2015), but also in established animal models such as chronic unpredictable stress (Hamani et al., 2012; Lim et al., 2015) and chronic social defeat stress (Veerakumar et al., 2014). However, DBS failed to treat learned helplessness (Hamani et al., 2010). Despite its increasing use, the precise mechanism of action of DBS is not fully understood. Depolarization blockade, hyperpolarization of cell bodies and dendrites, neurotransmitter depletion and/or synaptic inhibition of afferent projections are among the mechanisms postulated (Lozano and Lipsman, 2013).

In an attempt to examine the short-term effects of DBS, we have recently demonstrated that DBS of the IL for 1 h elevated the efflux of glutamate and serotonin (5-HT) in the medial prefrontal cortex (mPFC). This was accompanied by an antidepressant-like response in the forced swim test (FST) that was reverted by systemic and intra-mPFC administration of NBQX, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist (Jiménez-Sánchez et al., 2015). Further, IL DBS substantially increased c-Fos formation in cortical and subcortical areas (Jiménez-Sánchez et al., 2015), which suggests a stimulation of the mPFC output, notably to the brainstem monoaminergic nuclei. Nevertheless, these changes in prefrontal transmitters were observed in naïve rats, and the occurrence of similar effects of short-term IL DBS on an animal model of depression were not established. To fill this gap, in the present work, we sought to examine the behavioral and biochemical (release of glutamate and 5-HT in the mPFC) consequences of IL DBS, both in sham rats and in an animal model of depression, i.e. the olfactory bulbectomized (OBX) rat. Although the typical hyperlocomotion of OBX rats might seem counterintuitive with symptoms of depression, other features of the model (e.g., anhedonia, deficits in social interaction) more recognizably resemble core characteristics of depressive states. Overall the OBX rat has been postulated to more accurately model depression with comorbid anxiety (Wang et al., 2007). Most notably OBX-induced hyperlocomotion is responsive to chronic, but not acute, treatment with antidepressants, which is supportive of predictive validity of the model and, under this condition, a response to short-term DBS might be relevant to a rapid antidepressant effect. In addition to behavioral and neurochemical readouts, the intracellular signaling pathways involved in the antidepressant-like effects of IL DBS were also examined.

2. Materials and methods

2.1. Animals and drugs

A total of 81 male Wistar rats weighing 290–370 g were divided in two experimental settings: microdialysis ($n = 40$) and behavioral/molecular ($n = 41$) studies. Food and water were always available *ad libitum*. All experimental procedures followed national (R.D. 53/2013) and European legislation (Directive, 2010/63/EU of the European Parliament and of the Council, 22 September 2010, on the protection of animals used for scientific purposes), and were approved by the Institutional Animal Care and Use Committee of the University of Cantabria, all efforts were made to minimize animal suffering and to reduce the number of animals used.

Glutamate, 5-hydroxytryptamine (5-HT) oxalate, veratridine, temsirolimus, and o-phthaldialdehyde (OPA) reagent (containing 1 mg OPA per ml solution with 2-mercaptoethanol as the sulphydryl moiety) were purchased from Sigma-Aldrich (Tres Cantos, Spain). Citalopram hydrobromide was purchased from Tocris (Bristol, UK). Temsirolimus (1 mg/kg) was dissolved in saline for intraperitoneal (i.p.) administration.

2.2. Deep brain stimulation

Bipolar stimulating electrodes were implanted bilaterally under pentobarbital anesthesia (60 mg/kg, i.p.) in the IL mPFC (AP +3.2 mm, L ±0.6 mm, DV -5.4 mm from bregma) according to Paxinos and Watson (2005). They consisted of two stainless steel enamel-coated wires (California Fine Wire, Grover Beach, CA) with a diameter of 150 μm and a tip separation of ~100 μm and *in vitro* impedances of 10–30 kΩ. The stimulation settings were similar to those proved to be efficaceous in depressive states (Mayberg et al., 2005), but adapted to the smaller size of the targeted area in the rat. Stimulation lasted for 1 h and its parameters were: frequency, 130 Hz; current intensity, 200 μA and pulse width, 90 μs. Continuous alternating current with biphasic square pulses was delivered with a CS-20 Stimulator (Cibertec, Madrid, Spain) attached to an overhead electrical swivel (Plastics One Inc, Roanoke, VA, USA). In control (sham) groups, all rats had the two electrodes implanted, but no current was delivered.

2.3. Intracerebral microdialysis

Concentric dialysis probes with a 4-mm membrane were implanted under sodium pentobarbital anesthesia (60 mg/kg i.p.) in the mPFC (AP +3.2 mm, L ±0.6 mm, DV -6.0 mm; from bregma), according to Paxinos and Watson (2005). One electrode was fixed to the dialysis probe and the other was implanted alone in the contralateral mPFC. Although we cannot attribute mPFC serotonin (or glutamate) release as pertaining to IL or prelimbic cortices, we have previously shown that the antidepressant-like effects of 1 h DBS are associated with increased extracellular serotonin and glutamate in the entire mPFC (Jiménez-Sánchez et al., 2015). Microdialysis experiments were conducted 48 h after surgery in freely moving rats by continuously perfusing probes with artificial cerebrospinal fluid (aCSF, 125 mM NaCl, 2.5 mM KCl, 1.26 mM $CaCl_2$, 1.18 mM $MgCl_2$, and 1 μM citalopram) at a rate of 1.5 μl/min. Dialysate samples of 30 μl were collected every 20 min, and 5-HT and glutamate were determined by HPLC as described (López-Gil et al., 2007). At the completion of the experiments, rats were given an overdose of sodium pentobarbital and brain tissue was processed according to standard procedures (cresyl violet staining) to verify the correct placement electrodes and/or dialysis probes. Data from rats with probes and/or electrodes incorrectly placed was disregarded.

2.4. Olfactory bulbectomy

The animals were anesthetized with isofluorane, carried in medical oxygen, induced at 5% and maintained at 1–2% concentrations at a flow rate of 2 l/min) and fixed on a stereotaxic apparatus. A midline sagittal incision was made to expose the skull and two 2-mm diameter holes were made 8 mm rostrally from bregma and 2 mm lateral from the midline. The olfactory bulbs were then suctioned through the holes using a vacuum pump and the cavity was filled with bone wax to control bleeding. Special care was taken to avoid damaging the frontal cortex. Sham-operated rats were subjected to a similar procedure, except that no brain tissue was removed. After a 4-week recovery period, an open field test was conducted as previously described under aversive conditions of high-luminosity (600–800 lx) (Mar et al., 2002; Rodríguez-Gaztelumendi et al., 2009) to confirm the characteristic bulbectomy-induced behavior (hyperactivity). The arena consisted of a 100 × 100 × 75 cm platform, which was divided into 10 × 10 cm squares. Each animal was placed in the center of the open field and the total number of peripheral and central squares crossed was recorded for a 3 min period. All measurements were carried out in a darkened room and after each test the open field

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