Journal of Affective Disorders 217 (2017) 80–88

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Increased dopamine receptor expression and anti-depressant response following deep brain stimulation of the medial forebrain bundle

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ARTICLE INFO

Keywords:
Deep brain stimulation
MFB
Depression
FST
Dopamine

ABSTRACT

Background: Among several potential neuroanatomical targets pursued for deep brain stimulation (DBS) for treating those with treatment-resistant depression (TRD), the superolateral-branch of the medial forebrain bundle (MFB) is emerging as a privileged location. We investigated the antidepressant-like phenotypic and chemical changes associated with reward-processing dopaminergic systems in rat brains after MFB-DBS.

Methods: Male Wistar rats were divided into three groups: sham-operated, DBS-Off, and DBS-On. For DBS, a concentric bipolar electrode was stereotactically implanted into the right MFB. Exploratory activity and depression-like behavior were evaluated using the open-field and forced-swimming test (FST), respectively. MFB-DBS effects on the dopaminergic system were evaluated using immunoblotting for tyrosine hydroxylase (TH), dopamine transporter (DAT), and dopamine receptors (D1-D5), and high-performance liquid chromatography for quantifying dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in brain homogenates of prefrontal cortex (PFC), hippocampus, amygdala, and nucleus accumbens (NAc).

Results: Animals receiving MFB-DBS showed a significant increase in swimming time without alterations in locomotor activity, relative to the DBS-Off ($p < 0.039$) and sham-operated groups ($p < 0.014$), indicating an antidepressant-like response. MFB-DBS led to a striking increase in protein levels of dopamine D2 receptors and DAT in the PFC and hippocampus, respectively. However, we did not observe appreciable differences in the expression of other dopamine receptors, TH, or in the concentrations of dopamine, DOPAC, and HVA in PFC, hippocampus, amygdala, and NAc.

Limitations: This study was not performed on an animal model of TRD.

Conclusion: MFB-DBS rescues the depression-like phenotypes and selectively activates expression of dopamine receptors in brain regions distant from the target area of stimulation.

1. Introduction

Major depressive disorder (MDD) is a chronic and disabling mental disorder with high amount of morbidity and shortened lifespan (De Hert et al., 2011; Ferrari et al., 2013; Whiteford et al., 2013). MDD patients display depressive mood, anhedonia, suicidal behavior, and other cognitive and somatic symptoms (Bostwick and Pankrazt, 2000; Leung et al., 2012; Charlson et al., 2013; Zarate et al., 2013). Despite the availability of several conventional antidepressant medications, the number of treatment refractory patients is increasing (Rush et al., 2006; Nierenberg et al., 2010; Romera et al., 2013). Thus, alternative therapeutic approaches are in high demand. In recent clinical trials, deep brain stimulation (DBS) ensued promising neuromodulatory effects in drug-resistant neuropsychiatric disorders like obsessive-compulsive disorder (OCD), Tourette syndrome, addiction, and MDD (Krack et al., 2010). Moreover, the substantial benefits of DBS for

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http://dx.doi.org/10.1016/j.jad.2017.03.074
Received 14 November 2016; Received in revised form 24 March 2017; Accepted 30 March 2017
Available online 05 April 2017

patients with severe neurological diseases like Parkinson's disease (PD), essential tremor, and motor symptoms of dystonia and dyskinesia are well recognized, as is its safety, and its use is approved by the US FDA (Kleiner-Fisman et al., 2006; Andrews, 2010; Mentzel al, 2012; Creed et al., 2013; Hariz et al., 2013; Kalia et al., 2013; Vidailhet et al., 2013).

Due to the reversible nature of DBS, it is an appealing surgical option for patients with treatment-resistant depression (TRD). In DBS, electrodes are stereotactically implanted in specific neuroanatomical targets where electrical stimulation is applied via a stimulator device placed subcutaneously (Tye et al., 2009). Multiple DBS targets for TRD have been pursued by various research consortiums with promising therapeutic effects seen in preclinical and clinical settings (Mayberg et al., 2005; Schlaepfer et al., 2008, 2013; Johansen-Berg et al., 2008; Malone et al., 2009; Bewernick et al., 2012). Among them, the superolateral branch of the medial forebrain bundle (MFB) is particularly intriguing, because this fiber bundle is connected with the reward-seeking and appetite motivation neurocircuitry at crucial distant sites including Brodmann area 25 of the subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), and anterior limb of the internal capsule (ALIC) (Coenen et al., 2011; Torres-Sanchez et al., 2016). The dopaminergic reward system has been implicated in the pathophysiology of MDD (Nestler et al., 2002; Nestler and Carlezon, 2006). Notably, in contrast to traditional antidepressant medications, MFB-DBS showed dramatic therapeutic response occurring within just days after initiation of stimulation (Schlaepfer et al., 2013; Fenoy et al., 2016). Galvez et al. (2015) extensively reviewed the vital structural and functional pathways originating from MFB that connect with different brain areas possibly involved in the pathogenesis of mood disorders. This neuroanatomical location has been designated as a privileged target for the beneficial neuromodulatory effect after DBS treatment for neuropsychiatric disorders, and suggests that dopamine is the substrate mediating the effect (Döbrössy et al., 2015). While neuromodulation through MFB is considered as a potential therapeutic strategy in the treatment of resistant MDD (Coenen et al., 2011; Schlaepfer et al., 2013; Döbrössy et al., 2015; Fenoy et al., 2016), further investigations concerning the network of depression using neuromodulation platforms in animal models might provide insight into the mechanism of treatment of MDD.

While MFB-DBS in rats is not a new therapeutic approach to study depression, the underlying neurobiological mechanisms of its effect are still not clear. In the present study, we sought to investigate the hypothesis that DBS of the MFB induces antidepressant-like effects in rats by activating the dopaminergic reward pathways in the rat brain. We delivered MFB-DBS and its effect on depression-like behavior was tested using the forced swimming test (FST), a main behavioral screening method that has proven predictive validity for DBS in rats (Temel et al., 2007; Hamani et al., 2010a, 2010b, 2014; Hamani and Nobrega, 2010, 2012; Hamani and Temel, 2012; Schlaepfer et al., 2013). It has been reported that MFB-DBS is effective for treating MDD because it activates the ventral tegmental area (VTA) via recruitment of descending glutamatergic fibers of the MFB and this might in turn change the fate of dopamine in the remote nodes of the network (Schlaepfer et al., 2013, 2014). Although no changes in monoamine levels were detected by microdialysis in the NAc after MFB-DBS (Bregman et al., 2015), dopamine's role in relieving the depressive phenotype following MFB-DBS is still inconclusive (Bregman et al., 2015; Furlanetti et al., 2016). Recently, ontogenetic activation of rat VTA dopaminergic neurons led to increased blood oxygen level-dependent (BOLD) signal on functional magnetic resonance imaging (fMRI) in the PFC concomitant with improvement in anhedonia (Ferenczi et al., 2016), further identifying dopamine as central to the neurocircuitry of reward. Therefore, additional mechanistic studies are required to ascertain potential substrates involved in the acute antidepressant-like effects of MFB-DBS. Herein, we have estimated the levels of dopamine receptors (D1 through D5), dopamine transporter (DAT), and tyrosine hydroxylase (TH) proteins using western blot technique and changes in content of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) employing high-performance liquid chromatography coupled with electrochemical detection (HPLC-ECD) in the prefrontal cortex (PFC), hippocampus, NAc and amygdala regions of rat brain. We selected these brain regions because MFB-DBS induces antidepressant-like effects and selectively modulates the neuronal activity in cortical and subcortical structures, PFC and NAc, which are involved in the underlying circuitry of depression (Hamani et al., 2014; Bregman et al., 2015).

2. Methods

2.1. Animals

Young adult male Wistar rats (n = 66), weighing 275–300 g at the beginning of the experiments, were housed at a temperature of 72–74°F and humidity of 46–54% with 12-h light dark cycle (lights on 06:00 h). The food and water were available ad libitum. All protocols were approved by the Institutional Animal Welfare Committee of the Center for Laboratory Animal Medicine and Care (CLAMC) for The University of Texas Health Science Center at Houston (UTHSC), Texas, USA. All possible efforts were made to reduce animal suffering and the number of animals used.

2.2. Study design

After 1 week of handling and acclimatization, the rats were divided into three different experimental groups: sham-operated, DBS-Off and DBS-On. The DBS-Off and DBS-On groups received unilateral stereotactic implantation of an electrode in the right MFB. Unilateral stimulation of MFB elicited immediate antidepressant response in human trials (Fenoy et al., 2016). A sham-operated group underwent the same surgery, which consisted of drilling burr holes in the skull in locations identical to those in the DBS-Off/On group but without placement of an electrode. Each group was further subdivided into two cohorts: one for assessment of the depression-like behavior using FST, and another for the spontaneous locomotor activity in open field test (OFT). All animals were allowed to recover for 7 days after implantation of electrodes. On day 8, groups of animals reserved for FST were subjected to the pretest session of 15 min, the detailed procedure of which is provided in the following Section 2.4.1. Immediately after this session, all animals in DBS-On and DBS-Off groups were connected with the DBS assembly. While DBS-On animals received continuous high frequency stimulation for 8 h (130 Hz, 200 μA amplitude, 90 μs pulse width), the DBS-off group was only connected to the stimulator wires without receiving any current. On the following day, the same animals again underwent 4 h of stimulation (DBS-On) or were connected to stimulator without stimulation (DBS-Off). Immediately thereafter they were subjected to behavioral testing using the FST. The time-frame of DBS was selected based on previous reports (Hamani et al., 2010a, 2010b, 2014; Edemann-Callesen et al., 2015) and on other literature showing that 1–2 doses of antidepressants after FST on day 1 and one dose before swimming on day 2 reduce immobility time in FST (Porsolt et al., 1978). The sham-operated animals were not exposed to the stimulation procedure. Similarly, DBS-On rats designated for the OFT were stimulated for 8 h on day 8 and 4 h on day 9, and thereafter subjected to the OFT. At the end of behavioral screening rats were euthanized and brain tissues were harvested for immunoblotting, HPLC and histological analyses.

2.3. Surgical procedures

Rats were anesthetized with inhaled 3% isoflurane and were maintained continuously throughout the surgery on a stereotaxic frame (Kopf Instruments, California, USA). The electrode was implanted unilaterally in the right MFB using the coordinates: 2.52 mm posterior to bregma, 1.7 mm right to midline, and 8 mm ventral to cortical