Brain Stimulation 8 (2015) 708–713

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

Antidepressant-like Effects of Medial Forebrain Bundle Deep Brain Stimulation in Rats are not Associated With Accumbens Dopamine Release

Tatiana Bregman [a], Roman Reznikov [a], Mustansir Diwan [a], Roger Raymond [a], Christopher R. Butson [b,c], José N. Nobrega [a], Clement Hamani [a,d,*]

[a] Behavioural Neurobiology Laboratory, Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, Canada M5T 1R8
[b] Department of Bioengineering, University of Utah, Salt Lake City, UT, USA
[c] Scientific Computing & Imaging Institute, University of Utah, Salt Lake City, UT, USA
[d] Division of Neurosurgery, Toronto Western Hospital, 399 Bathurst Street, Toronto, ON, Canada M5T 2S8

ARTICLE INFO

Article history:
Received 5 November 2014
Received in revised form
13 January 2015
Accepted 21 February 2015
Available online 30 March 2015

Keywords:
Medial forebrain bundle
Depression
Deep brain stimulation
Nucleus accumbens
Dopamine
Serotonin
Stimulation

ABSTRACT

Background: Medial forebrain bundle (MFB) deep brain stimulation (DBS) is currently being investigated in patients with treatment-resistant depression. Striking features of this therapy are the large number of patients who respond to treatment and the rapid nature of the antidepressant response.
Objective: To study antidepressant-like behavioral responses, changes in regional brain activity, and monoamine release in rats receiving MFB DBS.
Methods: Antidepressant-like effects of MFB stimulation at 100 μA, 90 μs and either 130 Hz or 20 Hz were characterized in the forced swim test (FST). Changes in the expression of the immediate early gene (IEG) *zif268* were measured with *in situ* hybridization and used as an index of regional brain activity. Microdialysis was used to measure DBS-induced dopamine and serotonin release in the nucleus accumbens.
Results: Stimulation at parameters that approximated those used in clinical practice, but not at lower frequencies, induced a significant antidepressant-like response in the FST. In animals receiving MFB DBS at high frequency, increases in *zif268* expression were observed in the piriform cortex, prelimbic cortex, nucleus accumbens shell, anterior regions of the caudate/putamen and the ventral tegmental area. These structures are involved in the neurocircuitry of reward and are also connected to other brain areas via the MFB. At settings used during behavioral tests, stimulation did not induce either dopamine or serotonin release in the nucleus accumbens.
Conclusions: These results suggest that MFB DBS induces an antidepressant-like effect in rats and recruits structures involved in the neurocircuitry of reward without affecting dopamine release in the nucleus accumbens.

Introduction

One potentially promising deep brain stimulation (DBS) target for the treatment of depression is the medial forebrain bundle (MFB). In a recent open label clinical trial, over 80% of treatment-refractory patients undergoing surgery showed a significant degree of improvement [1]. In contrast to medications, the initial therapeutic response to MFB DBS was quite dramatic, occurring within days after stimulation onset [1]. The rationale for conducting MFB DBS in depression stems from imaging studies originally carried out in patients with Parkinson's disease (PD) treated with subthalamic nucleus (STN) stimulation [2]. Commonly reported side effects when STN electrodes are misplaced medially include dysphoria and mania [3,4]. While these have initially been attributed to the stimulation of medial regions of the limbic STN, Coenen and colleagues have argued that such psychiatric responses could be attributed to the stimulation of the MFB [2,5,6]. Using diffusion tensor imaging and tractography, the authors described a

Conflict of interest: CH is a consultant for St Jude Medical. CB is a consultant for St Jude Medical, Medtronics and Boston Scientific.

Disclosure: This study was supported by a grant received from St. Jude Medical. The sponsoring organization had no role in study design or the analysis of data.

* Corresponding author. Neuroimaging Research Section, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, M5T 1R8, Canada. Tel.: +1 416 5358501.
E-mail address: Clement.Hamani@camh.ca (C. Hamani).

http://dx.doi.org/10.1016/j.brs.2015.02.007
1935-861X/

tract departing the midbrain that bifurcated into inferomedial and superolateral branches [5]. The former approximated the one described as the MFB in rodents.

Experiments involving stimulation of the MFB were first conducted in the 50s by Olds and Milner and highlighted the hedonic-like effects that stimulation in this area could produce in rodents [7–9]. Over the years, protocols have been perfected so that rats and mice would reliably self-administer electrical current into this target [10]. With a strong hedonic component, self-stimulation has been a commonly used model to investigate mechanisms of reward and drug addiction [10–12].

A major difference between protocols used during DBS and self-stimulation is the continuous and prolonged administration of current (weeks/months) in the former [13,14] and the use of short bursts lasting less than a second over periods of minutes/hours in the latter [10]. In addition, self-stimulation has been used in preclinical research to mimic reward/hedonic states and not depressive-like behavior.

In the present study, we delivered MFB DBS at settings that parallel those used in the clinic to rats undergoing the forced swim test (FST), a paradigm that has been shown to have good predictive validity to screen antidepressant therapies [13–15]. Thereafter, we examined neurocircuitry changes and neurotransmitter release following MFB DBS.

Materials and methods

All protocols were approved by the Animal Care committee of the Centre for Addiction and Mental Health and are in accordance with the guidelines of the Canadian Council on Animal Care (CCAC).

Surgical procedures

Adult male Sprague–Dawley rats (250–300 g; Charles River) were anesthetized with isofluorane and had their heads fixed to a stereotaxic frame (David Kopf Instruments). Insulated stainless steel electrodes (250 μm diameter with 0.75 mm of exposed surface) were bilaterally implanted into the MFB and used as cathodes (anteroposterior −2.6, lateral ± 2.2, and depth 8.0 mm) [16]. Electrodes with similar characteristics attached to epidural screws were used as anodes. After being connected to a plastic pedestal (Plastics One), electrodes were fixed to the skull with dental acrylic cement. Controls had holes drilled to the skull but were not implanted with electrodes.

Forced swim test and electrical stimulation

Behavioral experiments were conducted seven days after surgery. On the first day of testing, rats were individually placed in a Plexiglas® cylinder filled with 25 ± 1 °C water. After 15 min of swimming, they received either continuous electrical stimulation or sham treatment for 4 h. On the second day, the same stimulation regimen was given to the animals for 2 h, followed by a second 5 min swimming session. During this session, immobility, swimming and climbing movements were scored by a blinded investigator, as previously described [17–19].

Stimulation was conducted with a handheld device (St Jude Medical model 3510, Plano, TX), connected to the animals through extension cables and a multi-channel commutator (Plastics One, Roanoke, VA). The following settings were tested: 100 μA, 90 μs of pulse width, and either 130 Hz (high frequency stimulation; HFS) or 20 Hz (low frequency stimulation; LFS). These settings were chosen based on our previous DBS studies in other targets [17–19]. In this protocol we did not use higher settings during behavioral studies, as MFB stimulation at currents above 300 μA was associated with stereotypic movements.

Open field test

Two days after the FST, animals received either stimulation or sham-treatment for 4 h. On the next day, the same treatment was provided for 2 h. Thereafter, locomotor activity was assessed for 30 min in a square 0.49 m^2 Plexiglas® open field apparatus (Med Associates) with infrared photo beams placed every 15 cm along the walls of the equipment. Crossing of the beams provided counts of motor activity.

Microdialysis

In a batch of animals not undergoing behavioral studies ($n = 5$), a microdialysis cannula was implanted into the right nucleus accumbens (AP + 1.8 mm, ML + or −2.4 mm, and DV −8 mm) along with bilateral MFB electrodes. Seven days later, animals were anesthetized with isofluorane. A microdialysis probe (MAB4.15.4, Scientific Products) was inserted into the target and perfused with Ringer's solution at a constant flow rate of 0.7 μL/min. Following an equilibration period (3 h), dialysate samples were collected every 30 min. Four baseline samples were collected over 2 h. The average of these measures was used as a single baseline value during analyses. Thereafter, animals received MFB stimulation at 100 μA 90 μs, 130 Hz for 1 h. Current was then increased to 500 μA (1 h collection). One hour after DBS offset, animals were given a single injection of amphetamine (3 mg/kg i.p.) as a positive control for the DBS experiment. One week later ($n = 4$), dialysis experiments were repeated with animals being injected with fenfluramine (10 mg/kg i.p.). Details on the monoamine assay and analysis of the samples have been previously described [20].

In situ hybridization and histology

One week after surgery, a batch of animals that did not undergo behavioral testing received stimulation for 4 h on day 1 and 2 h on day 2. Immediately after stimulation offset, animals were sedated using ketamine/xylazine anesthesia and sacrificed by decapitation. Hybridization was performed using ^{35}S-UTP labeled riboprobes complementary to *zif268*, as previously described [17,21]. After hybridization, slides were exposed to Kodak BioMax film for 6 days at 4 °C along with calibrated radioactivity standards. Film analyses were conducted with an MCID system (Interfocus, UK). In this study, the expression of *zif268* was measured in regions implicated in psychiatric disorders (Table 1). 3D modeling of structures expressing *zif268* was conducted as previously described [17]. To assess electrode placement, brains were stained with cresyl violet (Fig. 1).

Statistical analysis

One-way ANOVA (Tukey post-hoc), repeated one-way ANOVA or Student's *t* test were used to compare behavioral, microdialysis and *zif268* data across groups.

Results

Behavioral tests

MFB DBS induced a significant antidepressant-like effect in the FST ($F(2,31) = 5.72$, $P = 0.008$ for immobility; $F(2,31) = 5.67$, $P = 0.008$ for swimming). Animals treated with 100 μA, 90 μs and

Table 1
zif268 expression in animals receiving medial forebrain bundle deep brain stimulation.

Region	Control	DBS	*P*
Pir	34.9 (1.9)	47.2 (2.4)	0.01
PL	20.4 (1.3)	25.1 (1.4)	0.04
AcbS	12.2 (1.0)	16.7 (1.4)	0.03
CPu ant	11.7 (0.7)	14.5 (0.9)	0.04
DGd	16.9 (0.7)	13.4 (0.9)	0.02
VTA	0.4 (0.2)	2.1 (0.6)	0.04
IL	15.3 (1.2)	16.4 (1.1)	0.52
CG1	17.3 (1.1)	20.8 (1.3)	0.08
CG2	18.9 (1.2)	21.0 (1.2)	0.27
AcbC	12.1 (1.0)	14.6 (1.1)	0.12
CPU DM	13.4 (1.2)	14.6 (1.2)	0.53
CPU DL	10.9 (1.0)	13.5 (1.0)	0.11
LS	11.2 (1.1)	11.5 (0.8)	0.80
VP	2.8 (0.9)	3.1 (0.7)	0.83
Me	7.1 (1.6)	5.6 (0.6)	0.40
Amg BL	9.0 (1.0)	8.1 (0.6)	0.48
Amg BM	7.4 (1.2)	7.4 (1.4)	0.99
LH	3.2 (1.1)	2.9 (0.9)	0.82
MD	2.3 (1.0)	2.6 (0.6)	0.80
DGv	4.2 (1.2)	3.4 (1.1)	0.66
CA1d	34.5 (2.0)	32.0 (1.3)	0.32
CA1v	2.2. (0.9)	2.2 (0.7)	0.98
CA3d	17.5 (1.8)	14.9 (0.8)	0.22
CA3v	1.6 (0.8)	1.4 (0.6)	0.82
LHb	2.9 (1.2)	3.0 (0.7)	0.97
SNr	1.0 (0.6)	0.7 (0.4)	0.77
SNc	0.9 (0.6)	0.8 (0.4)	0.87
DMPAG	2.5 (1.0)	3.6 (1.2)	0.51
LPAG	2.0 (1.0)	2.0 (0.7)	0.98
DRnd	2.0 (1.1)	3.2 (0.9)	0.42
DRnv	1.6 (0.8)	1.4 (0.8)	0.87
MRn	2.3 (1.0)	2.4 (0.9)	0.94
LC	1.9 (0.8)	1.7 (0.7)	0.91

Values represent average measures in microCuries/gram (SE). Pir—piriform cortex; PL—prelimbic cortex; AcbS—nucleus accumbens shell; CPU ant—caudate putamen anterior; DGd—dentate gyrus dorsal; VTA—ventral tegmental area; IL—infralimbic cortex; Cg1—Cingulate gyrus, area 1; Cg2—Cingulate gyrus, area 2; AcbC—nucleus accumbens core; CPU DM—caudate putamen dorsomedial; CPU DL—caudate putamen dorsolateral; LS—lateral septum; VP—ventral pallidum; Amg Me—amygdala medial nucleus; Amg BL—amygdala basolateral nucleus; Amg BM—amygdala basomedial nucleus; LH—lateral hypothalamus; MD—mediodorsal nucleus of the thalamus; DGv—dentate gyrus ventral; CA1d—CA1 dorsal; CA1v—CA1 ventral; CA3d—CA3 dorsal; CA3v—CA3 ventral; LHb—Lateral habenula; SNr—substantia nigra reticulata; SNc—substantia nigra compacta; DMPAG—dorsomedial periaqueductal grey; LPAG—lateral periaqueductal grey; DRnd—dorsal raphe nucleus dorsal; DRnv—dorsal raphe nucleus ventral; MRn—medial raphe nucleus; LC—locus ceruleus.

130 Hz ($n = 10$) had a 30% decrease in immobility scores as compared to controls ($n = 14$; $P = 0.008$; Fig. 2A). In animals receiving DBS at 20 Hz ($n = 10$), reduction in immobility was in the order of 20% ($P = 0.1$).

To assess whether the observed effects of DBS were due to simple locomotor changes, MFB stimulation was delivered to animals during open field testing. No differences were found between animals treated with DBS at 130 Hz ($n = 8$) or 20 Hz ($n = 7$) and non-stimulated controls ($n = 6$; $F(2,18) = 0.32$, $P = 0.7$; Fig. 2B).

Immediate early gene expression

In animals receiving DBS, significant increases in *zif268* expression were detected in the piriform cortex, prelimbic cortex, shell of the nucleus accumbens, anterior striatum and ventral tegmental area (Fig. 3, Table 1). In contrast, *zif268* mRNA levels in stimulated animals were reduced in the dentate gyrus of the dorsal hippocampus.

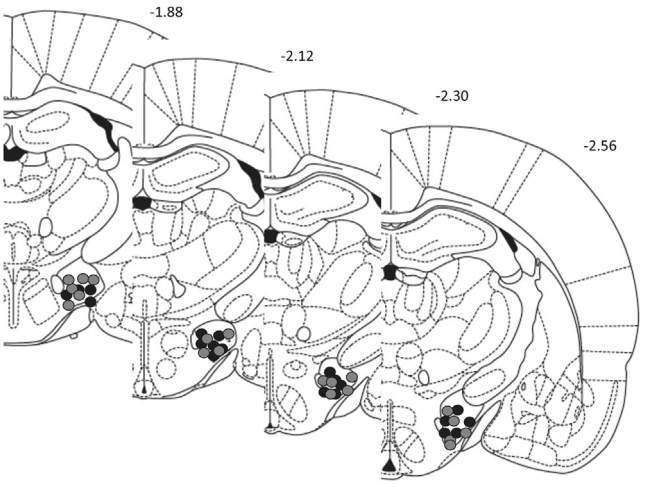

Figure 1. Location of DBS electrodes implanted in the region of the medial forebrain bundle in animals undergoing behavioural testing. Schematic representation of coronal brain sections showing the region in which electrode tips were identified. Dark and grey circles represent animals given DBS at 130 Hz or 20 Hz, respectively. Right and left electrodes were plotted in the same hemisphere for clarity. Numbers in the right upper corner denote distance from bregma. Permission to reprint the figures from The Rat Brain in Stereotaxic Coordinates; Authors: George Paxinos and Watson; Copyright (1998) granted by Elsevier.

Microdialysis

MFB DBS induced no changes in dopamine ($F(6,24) = 2.3$; $P = 0.20$) or serotonin release ($F(6,18) = 1.1$; $P = 0.38$) at either 100 μA or 500 μA (Fig. 4; comparison of baseline, DBS and post stimulation periods). As a positive control, animals were given single injections of amphetamine or fenfluramine. After the administration of the former, levels of dopamine in the nucleus

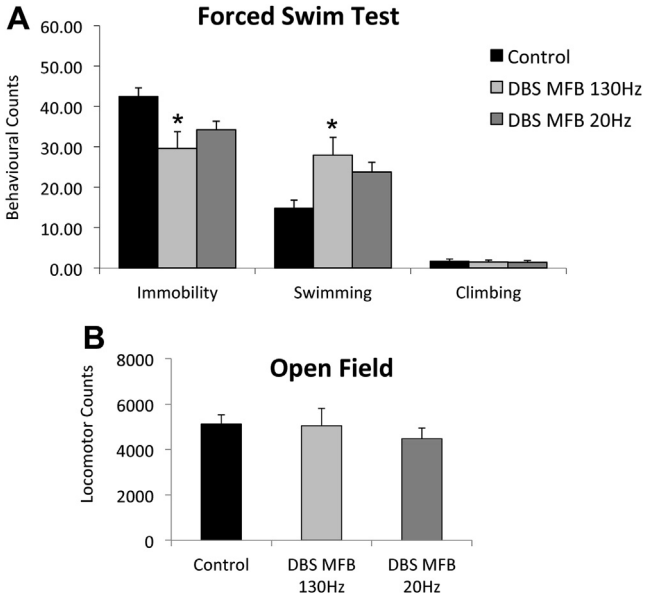

Figure 2. Behavioural response of medial forebrain bundle DBS in the forced swim test (FST) and open field. (A) In the FST, animals receiving DBS at 130 Hz ($n = 10$) showed a significant reduction in immobility ($P = 0.008$) and an increase in swimming ($P = 0.009$) as compared to controls ($n = 14$). In contrast, the antidepressant-like effects of DBS at 20 Hz were not statistically significant ($n = 10$). (B) In the open field, locomotor activity was measured during 30 min with no differences being recorded across groups. Data represent means ± SEM.

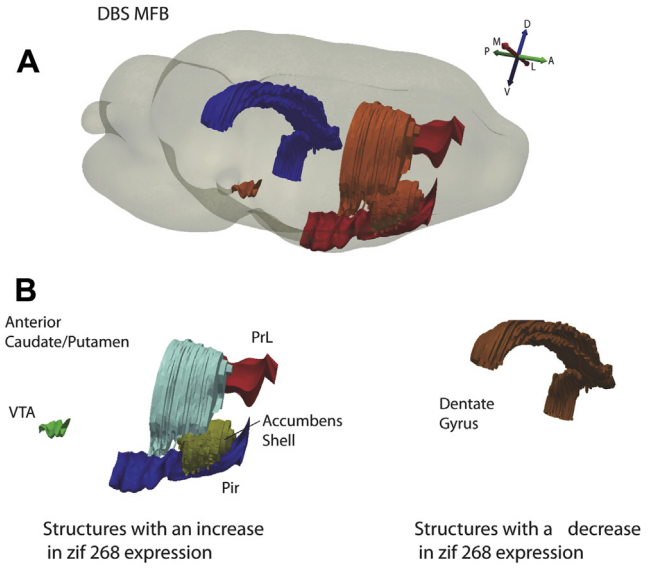

Figure 3. Differences in *zif268* expression between controls and animals receiving medial forebrain bundle DBS. (A) In the upper panel, 3D reconstructions give an overview of structures with an increase (red for cortical and orange for subcortical) or a decrease (blue) in *zif268* expression after DBS. (B) In the lower panel, individually labeled structures are represented in different colors. Pir- Piriform cortex; PrL- Prelimbic cortex; VTA- Ventral tegmental area.

accumbens were increased by approximately 22 fold (Fig. 4A; $F(4,16) = 11.3$; $P = 0.02$; comparison of baseline and drug injection samples). After fenfluramine, serotonin levels were increased by 4.5 fold (Fig. 4B; $F(4,12) = 6.4$; $P = 0.03$; comparison of baseline and drug injection samples).

Discussion

Our findings suggest that MFB DBS induces frequency-dependent antidepressant-like effects in the FST and modulates activity in structures that project to or receive projections from the MFB. In contrast to self-stimulation studies [22–25], no significant dopamine or serotonin release was detected during stimulation at the settings used in our experiments.

Over 50 structures within the brainstem, hypothalamus, thalamus, basal ganglia, basal forebrain and cortex send their axons through the MFB [26,27]. Perhaps the most thoroughly characterized of these connections is the pathway that projects from the VTA to the nucleus accumbens. These fibers are crucial for prediction of reward and for maintenance of a normal hedonic state [28–31]. In addition, fibers in the VTA-Acb pathway are thought to play a role in mechanisms of addiction and schizophrenia [32].

Since the original work by Olds and Milner, electrical stimulation has been applied to various brain sites in order to map reward-processing areas [7–9]. Robust behavioral responses have been described with current applied to the septal area, cingulate cortex, MFB, among others [7–9]. At present, self-stimulation of the MFB is a well-characterized paradigm to study hedonic states and mechanisms of reward. Typical anatomical target, current and frequency are similar to those applied in our DBS study, except for the fact that our stimulation was continuous and self stimulation is applied in a cyclic on/off mode [10]. In one of the few studies in which DBS was co-administered with self-stimulation, the administration of current to the ventromedial prefrontal cortex of Flinders rats was shown not to have an anti-anhedonic-like effect [33]. We have made similar observations in Sprague–Dawley rats (data not shown).

Since self-stimulation of the MFB induces hedonic-like responses and dopaminergic fibers run through this pathway, stimulation-induced release in dopamine has been postulated as a potential mechanism for the hedonic-like effects of self-stimulation. Whether this is actually the case, however, is still debatable. While some studies have indeed reported that self-stimulation induces dopamine release [22–25,34], others have suggested that a high dopamine turnover was equally important for the behavioral effects observed in rats [23].

It is quite conceivable that mechanisms other than a simple increase in dopamine release may be responsible for the behavioral responses of self-stimulation. The vast majority of axons running through the MFB are non-myelinated. Of those, only 0.2% are dopaminergic [35]. Both self-stimulation and DBS are often delivered at high frequencies (e.g. 100–140 Hz) [10,14]. The only neural elements capable of following stimulation at such settings are myelinated axons. In addition, when the chronaxie of fibers is considered, DA pathways are more easily recruited with pulse widths in the order of 500 μs (i.e. much longer than the 100 μs used in our study) [36]. Even when optimal settings for stimulating non-myelinated fibers are used, it is 3–6 times harder to recruit non-myelinated DA axons than non-DA myelinated ones [35]. In this context, it is not surprising that MFB DBS did not induce dopamine release in our study. That said, it is possible that different results might have been attained with the use of smaller electrode tips, a

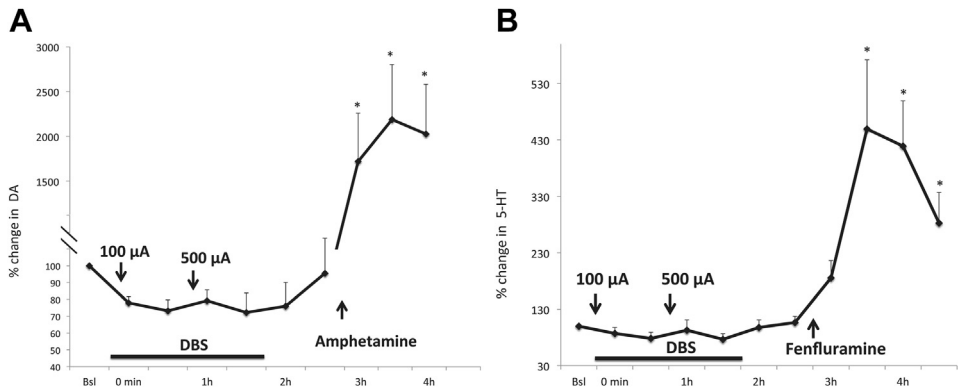

Figure 4. Monoamine release during medial forebrain bundle DBS. No significant changes in dopamine (A) or serotonin (B) levels were observed when samples obtained during stimulation were compared to those at baseline. In contrast, significant increases in dopamine or serotonin have been recorded after single doses of amphetamine 3 mg/kg (A) or fenfluramine 10 mg/kg (B), respectively. Samples were collected every 30 min. Bsl-average of four baseline samples collected 2 h before the experiments. Horizontal bar represents the interval during which DBS was administered. * Significantly different from Bsl at $P < 0.05$.

higher charge density, the delivery of stimulation bursts, or DBS conducted in other regions of the MFB [34,35].

We chose to implant MFB electrodes near the lateral hypothalamus since this is the most commonly used target for self-stimulation and the region where the bundle is most prominent. In the clinic, the target used for DBS is more posterior, closer to the VTA. Our rationale for not selecting this target was threefold: 1) Near the brainstem, the MFB is small and difficult to isolate (i.e. stimulation would have certainly spilled over to other structures that might have influenced results). 2) The likelihood of animals developing side effects at relatively low settings with electrodes implanted in the brainstem would have been higher (as observed in humans). 3) Dopaminergic pathways of the mesolimbic and mesostriatal systems run through the MFB at the level of the lateral hypothalamus (e.g. injections of toxins into the MFB to induce parkinsonism in rats are conducted at the level of the lateral hypothalamus) [37]. Though the spread of current to the lateral hypothalamus has likely occurred in our study, similarities between effects recorded in animals and humans suggest that a common element – the MFB – may have likely been important for an antidepressant-like response.

Structures recruited in the region of the MFB during self-stimulation have been previously examined using functional markers such as cytochrome oxidase and 2-deoxyglucose [38,39]. Similar to our findings, those studies have also shown increased activity in brain regions involved in mechanisms of reward (e.g. prelimbic cortex and nucleus accumbens) [38,39]. Thus, although MFB stimulation does not appear to induce its antidepressant-like effect by activating ascending dopaminergic fibers, it remains possible that it affects the accumbens via VTA-PFC projections. In this case, the primary effect of stimulation might be on descending afferents to the VTA rather than on efferents from the VTA. This could be tested by investigating the effects of MFB DBS after lesioning or inactivating the VTA, the PFC, or the accumbens itself.

One of the common features between MFB stimulation and DBS applied to other targets (e.g. vmPFC, nucleus accumbens and white matter fibers of forceps minor) is an increased expression of IEGs in the piriform cortex [17]. This structure is part of the olfactory system and also seems to be involved in medication-induced antidepressant-like responses observed in the FST [40,41]. Future studies are still needed to better ascertain the role of the piriform cortex in depression.

In summary, our results suggest that MFB DBS induces frequency-dependent antidepressant-like effects in the FST. In addition, we found that this therapy increases the expression of IEGs in various structures involved in the neurocircuitry of reward that project to, or receive projections from, the MFB. As no changes in monoamine levels were detected after DBS, additional mechanisms need to be explored to ascertain potential substrates involved in the acute antidepressant-like effects of MFB DBS.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2015.02.007.

References

[1] Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry 2013;73:1204–12.

[2] Coenen VA, Honey CR, Hurwitz T, et al. Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. Neurosurgery 2009;64:1106–14. discussion 1114–1105.

[3] Castrioto A, Lhommee E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol 2014;13:287–305.

[4] Deuschl G, Paschen S, Witt K. Clinical outcome of deep brain stimulation for Parkinson's disease. Handb Clin Neurol 2013;116:107–28.

[5] Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci 2012;24:223–36.

[6] Coenen VA, Schlaepfer TE, Maedler B, Panksepp J. Cross-species affective functions of the medial forebrain bundle-implications for the treatment of affective pain and depression in humans. Neurosci Biobehav Rev 2011;35:1971–81.

[7] Beninger RJ, Bellisle F, Milner PM. Schedule control of behavior reinforced by electrical stimulation of the brain. Science 1977;196:547–9.

[8] Szabo I, Milner PM. Self-stimulation in rats: tip alignment influences the effectiveness of bipolar electrodes. Brain Res 1972;48:243–50.

[9] Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 1954;47:419–27.

[10] Carlezon Jr WA, Chartoff EH. Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. Nat Protoc 2007;2:2987–95.

[11] Koob GF. Neural mechanisms of drug reinforcement. Ann N Y Acad Sci 1992;654:171–91.

[12] Wise RA. Addictive drugs and brain stimulation reward. Annu Rev Neurosci 1996;19:319–40.

[13] Hamani C, Nobrega JN. Preclinical studies modeling deep brain stimulation for depression. Biol Psychiatry 2012;72:916–23.

[14] Hamani C, Temel Y. Deep brain stimulation for psychiatric disease: contributions and validity of animal models. Sci Transl Med 2012;4(142):142rv8.

[15] Hamani C, Nobrega JN. Deep brain stimulation in clinical trials and animal models of depression. Eur J Neurosci 2010;32:1109–17.

[16] Paxinos G, Watson C. The rat brain in stereotaxic coordinates. Academic Press; 1998.

[17] Hamani C, Amorim BO, Wheeler AL, et al. Deep brain stimulation in rats: different targets induce similar antidepressant-like effects but influence different circuits. Neurobiol Dis 2014;71C:205–14.

[18] Hamani C, Diwan M, Isabella S, Lozano AM, Nobrega JN. Effects of different stimulation parameters on the antidepressant-like response of medial prefrontal cortex deep brain stimulation in rats. J Psychiatr Res 2010;44:683–7.

[19] Hamani C, Diwan M, Macedo CE, et al. Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. Biol Psychiatry 2010;67:117–24.

[20] Creed MC, Hamani C, Bridgman A, Fletcher PJ, Nobrega JN. Contribution of decreased serotonin release to the antidyskinetic effects of deep brain stimulation in a rodent model of tardive dyskinesia: comparison of the subthalamic and entopeduncular nuclei. J Neurosci 2012;32:9574–81.

[21] Creed MC, Hamani C, Nobrega JN. Early gene mapping after deep brain stimulation in a rat model of tardive dyskinesia: comparison with transient local inactivation. Eur Neuropsychopharmacol 2012;22:506–17.

[22] Hernandez G, Hamdani S, Rajabi H, et al. Prolonged rewarding stimulation of the rat medial forebrain bundle: neurochemical and behavioral consequences. Behav Neurosci 2006;120:888–904.

[23] Nakahara D, Fuchikami K, Ozaki N, Iwasaki T, Nagatsu T. Differential effect of self-stimulation on dopamine release and metabolism in the rat medial frontal cortex, nucleus accumbens and striatum studied by in vivo microdialysis. Brain Res 1992;574:164–70.

[24] Yavich L, Tanila H. Mechanics of self-stimulation and dopamine release in the nucleus accumbens. Neuroreport 2007;18:1271–4.

[25] You ZB, Chen YQ, Wise RA. Dopamine and glutamate release in the nucleus accumbens and ventral tegmental area of rat following lateral hypothalamic self-stimulation. Neuroscience 2001;107:629–39.

[26] Nieuwenhuys R, Geeraedts LM, Veening JG. The medial forebrain bundle of the rat. I. General introduction. J Comp Neurol 1982;206:49–81.

[27] Veening JG, Swanson LW, Cowan WM, Nieuwenhuys R, Geeraedts LM. The medial forebrain bundle of the rat. II. An autoradiographic study of the topography of the major descending and ascending components. J Comp Neurol 1982;206:82–108.

[28] Baik JH. Dopamine signaling in reward-related behaviors. Front Neural Circuits 2013;7:152.

[29] Glimcher PW. Understanding dopamine and reinforcement learning: the dopamine reward prediction error hypothesis. Proc Natl Acad Sci U S A 2011;108(Suppl. 3):15647–54.

[30] Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci 2008;10:291–9.

[31] Schultz W. Updating dopamine reward signals. Curr Opin Neurobiol 2013;23:229–38.

[32] Tritsch NX, Sabatini BL. Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron 2012;76:33–50.

[33] Rea E, Rummel J, Schmidt TT, et al. Anti-anhedonic effect of deep brain stimulation of the prefrontal cortex and the dopaminergic reward system in a genetic rat model of depression: an intracranial self-stimulation paradigm study. Brain Stimul 2014;7:21–8.

[34] Miliaressis E, Emond C, Merali Z. Re-evaluation of the role of dopamine in intracranial self-stimulation using in vivo microdialysis. Behav Brain Res 1991;46:43–8.
[35] Yeomans JS. Two substrates for medial forebrain bundle self-stimulation: myelinated axons and dopamine axons. Neurosci Biobehav Rev 1989;13:91–8.
[36] Grace AA, Bunney BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons–1. Identification and characterization. Neuroscience 1983;10:301–15.
[37] Deumens R, Blokland A, Prickaerts J. Modeling Parkinson's disease in rats: an evaluation of 6-OHDA lesions of the nigrostriatal pathway. Exp Neurol 2002;175:303–17.
[38] Bielajew CH. Distribution of cytochrome oxidase in response to rewarding brain stimulation: effect of different pulse durations. Brain Res Bull 1991;26:379–84.
[39] Bielajew CH, Harris T. Self-stimulation: a rewarding decade. J Psychiatry Neurosci 1991;16:109–14.
[40] Jang DP, Lee SH, Park CW, Lee SY, Kim YB, Cho ZH. Effects of fluoxetine on the rat brain in the forced swimming test: a [F-18]FDG micro-PET imaging study. Neurosci Lett 2009;451:60–4.
[41] Sairanen M, O'Leary OF, Knuuttila JE, Castren E. Chronic antidepressant treatment selectively increases expression of plasticity-related proteins in the hippocampus and medial prefrontal cortex of the rat. Neuroscience 2007;144:368–74.