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Review

Cellular and molecular mechanisms triggered by Deep Brain Stimulation in depression: A preclinical and clinical approach

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ABSTRACT

Deep Brain Stimulation (DBS) was originally developed as a therapeutic approach to manage movement disorders, in particular Parkinson's Disease. However, DBS also seems to be an effective treatment against refractory depression when patients fail to respond satisfactorily to conventional therapies. Thus, DBS targeting specific brain areas can produce an antidepressant response that improves depressive symptomatology, these areas including the subcallosal cingulate region, nucleus accumbens, ventral capsule/ventral striatum, medial forebrain bundle, the inferior thalamic peduncle and lateral habenula. Although the efficacy and safety of this therapy has been demonstrated in some clinical trials and preclinical studies, the intrinsic mechanisms underlying its antidepressant effect remain poorly understood. This review aims to provide a comprehensive overview of DBS, focusing on the molecular and cellular changes reported after its use that could shed light on the mechanisms underpinning its antidepressant effect. Several potential mechanisms of action of DBS are considered, including monoaminergic and glutamatergic neurotransmission, neurotrophic and neuroinflammatory mechanisms, as well as potential effects on certain intracellular signaling pathways. Although future studies will be necessary to determine the key molecular events underlying the antidepressant effect of DBS, the findings presented provide an insight into some of its possible modes of action.

Contents

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; ACTH, adrenocorticotropic hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; DBS, Deep Brain Stimulation; CaMKII, calcium/calmodulin-dependent protein kinase type II; CREB, cAMP-response element binding; CSDS, chronic social defeat stress; CUMS, chronic unpredictable mild stress; DOPAC, 3,4-dihydroxyphenylacetic acid; DR, dorsal raphe; DSP-4, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; ERK, extracellular signal-regulated kinase; FST, forced swimming test; GABA, γ-aminobutyric acid; GSK3, glycogen synthase kinase 3; HAB, high anxiety-related behavior; HVA, homovanillic acid; LHb, lateral habenula; MDD, Major Depressive Disorder; MFB, medial forebrain bundle; mTOR, mammalian target of rapamycin; NA, noradrenaline; NAc, nucleus accumbens; PFC, prefrontal cortex; PI3K, phosphatidyl inositol-3 kinase; SCC, subcallosal cingulate region; TH, tyrosine hydroxylase; VC/VS, ventral capsule/ventral striatum; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

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1. Introduction

Major Depressive Disorder (MDD) represents one of the most disabling disorders worldwide (World Health Organization, 2011), with a global prevalence of around 4.7% (Ferrari et al., 2013). Many individuals that suffer from this neuropsychiatric illness are successfully managed using different therapies, which logically include antidepressant drugs and psychotherapy but that also include physical treatments. Despite the variety of therapeutic approaches available, unfortunately 30 to 40% of patients do not respond to first-line treatments and between 5 to 10% do not respond to any conventional therapy (Frank et al., 1991; Warden et al., 2007), indicating that a considerable number of patients fail to achieve sustained remission (Fava, 2003; Rush et al., 2006). Accordingly, MDD represents a significant economic burden that is associated with a severe loss in quality of life, intense personal suffering, and a higher risk of relapse and suicide (Hawton et al., 2013; Moussavi et al., 2007; Murray & Lopez, 1996). These data highlight the need to find new therapeutic approaches focused especially on these refractory patients.

In this context, Deep Brain Stimulation (DBS) is an innovative physical treatment against refractory MDD (Malone et al., 2009; Mayberg et al., 2005; Schlaepfer et al., 2013), a technique that has been used successfully for years to treat neurological disorders like Parkinson's disease (Benabid, 2003). Indeed, DBS is currently also being tested in psychiatric illnesses other than depression, such as Obsessive-Compulsive Disorder or addition (Holtzheimer & Mayberg, 2011; Luigjes et al., 2012). However, most studies into DBS for MDD have focused on its efficiency and efficacy, or improvements in the technique, while very few of them have set out to determine the intrinsic mechanisms involved in the beneficial effects of DBS, such as the neuronal networks, neurotransmitter systems, receptors or even the possible changes in intracellular signaling induced by DBS. Thus, it is now of interest to determine the cellular and molecular mechanism affected by DBS, not only to understand its efficacy but also to propose new mechanisms of action for future antidepressant approaches.

2. The sites of brain stimulation

2.1. Studies in humans

From a neuroanatomical perspective, the site of brain stimulation is essential to attain satisfactory antidepressant effects. Based on their involvement in the pathophysiology of depression, different areas have been selected as putative targets for treating this disorder (Schlaepfer et al., 2013; Drevets et al., 1998; Galvez et al., 2015; Morishita et al., 2014; Sartorius & Henn, 2007). Thus, in the first clinical trial the electrodes were placed in the subcallosal cingulate region (SCC), leading to a notable sustained antidepressant response (Mayberg et al., 2005). Indeed, the efficacy and safety of DBS applied to this area was since confirmed in other clinical trials (Holtzheimer et al., 2012; Kennedy et al., 2011; Lozano et al., 2008; Puigdemont et al., 2012). Likewise, other areas for stimulation have been proposed and also produce a promising improvement in depressive symptoms. Accordingly, the efficacy of DBS for MDD has since been demonstrated by targeting: the nucleus accumbens (NAc) or ventral capsule/ventral striatum (VC/VS) (Malone et al., 2009; Bewernick et al., 2010; Schlaepfer et al., 2008); the medial forebrain bundle (MFB, ascending ventral mesencephalic dopamine fibers from the ventral tegmental area – VTA) (Schlaepfer et al., 2013; Coenen et al., 2011); the inferior thalamic peduncle (Jimenez et al., 2013; Jimenez et al., 2005) and the lateral habenula (LHb) (Sartorius et al., 2010; Schneider et al., 2013). In addition, some commonly used MDD targets have also been used to treat other mental illnesses (Luigjes et al., 2012; Lipsman & Lozano, 2014) and for instance, DBS of the VC/VS is thought to be effective for the treatment of Obsessive-Compulsive Disorder (Greenberg et al., 2010).

2.2. Studies in animals

Although more clinical research is necessary to identify the optimal DBS targets in order to achieve a successful response in MDD patients, DBS experiments in human subjects are ethically self-limiting. For this reason, experimental animal models of depression which mimic certain physiological, endocrine and behavioral aspects observed in depressive patients are a convenient and widely-used alternative to address this (Bravo et al., 2009). However, because of the unique and complex features of human depression, the translation of data from animal models to human must be considered cautiously. DBS has been shown to revert depressive-like behavior in animal models of depression (Edemann-Callesen et al., 2015; Gersner et al., 2010; Hamani et al., 2012; Li et al., 2011; Meng et al., 2011; Schmuckermair et al., 2013; Veerakumar et al., 2014; Lim et al., 2015a). Thus, DBS of the ventromedial prefrontal cortex (vmPFC), the closest anatomic correlate in rodents of the SCC area in humans, was seen to induce an antidepressant-like effects in several tests, including the forced swimming test (FST), the sucrose preference test or the novelty suppressed feeding test (Lim et al., 2015a; Hamani et al., 2014; Hamani et al., 2010a; Hamani et al., 2010b; Jimenez-Sanchez et al., 2016a; Lim et al., 2015b; Perez-Caballero et al., 2014). Moreover, DBS in the same target reversed the depressive phenotype induced by chronic unpredictable mild stress (CUMS), chronic social defeat stress (CSDS) and olfactory bulbectomy, and that in a depressive rat line (Gersner et al., 2010; Hamani et al., 2012; Veerakumar et al., 2014; Lim et al., 2015a; Jimenez-Sanchez et al., 2016a; Moshe et al., 2016). In addition, an antidepressant-like effect was obtained when DBS was applied to the NAc in naïve and animals subjected to CUMS (Gersner et al., 2010; Lim et al., 2015a; Hamani et al., 2014; Lim et al., 2015b). Similar results were found in the high anxiety-related behavior (HAB) mouse model and in a model based on chronic adrenocorticotropic hormone (ACTH) administration (Schmuckermair et al., 2013; Kim et al., 2016), both models that are resistant to standard antidepressant therapies (Iijima et al., 2010; Landgraf et al., 2007). Similarly, LHb DBS had an antidepressant-like effect in the FST and it reversed the depressive-like behavior induced by CUMS, chronic ACTH administration and learned helplessness (Li et al., 2011; Meng et al., 2011; Lim et al., 2015a; Kim et al., 2016). Additionally, DBS of the MFB produced an antidepressant response in both naïve animals and in the Flinders Sensitive Line a genetic animal model of depression (Overstreet & Wegener, 2013) when assessed with the FST (Edemann-Callesen et al., 2015; Bregman et al., 2015).

3. Possible mechanisms involved in the effect of DBS on depression

Several attempts have been made to elucidate the cellular and molecular mechanisms involved in the antidepressant effect of DBS. Indeed, many reports have described the modulation of potential