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Review

Electrical stimulation of the medial forebrain bundle in pre-clinical studies of psychiatric disorders

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ABSTRACT

Modulating neuronal activity by electrical stimulation has expanded from the realm of motor indications into the field of psychiatric disorders in the past 10 years. The medial forebrain bundle (MFB), with a seminal role in motor, reward orientated and affect regulation behaviors, and its afferent and efferent loci, have been targeted in several DBS trials in patients with psychiatric disorders. However, little is known about the consequences of modulating the MFB in affective disorders. The paper reviews the relevant pre-clinical literature investigating electrical stimulation of regions associated with the MFB in the context of several models of psychiatric disorders, in particular depression. The clinical data is promising but limited, and pre-clinical studies are essential for improved understanding of the anatomy, the connectivity, and the consequences of stimulation of the MFB and regions associated with the neurocircuitry of psychiatric disorders. Current data suggests that the MFB is at a "privileged" position on this circuitry and its stimulation can simultaneously modulate activity at other key sites, such as the nucleus accumbens, the ventromedial prefrontal cortex or the ventral tegmental area. Future experimental work will need to shed light on the anti-depressive mechanisms of MFB stimulation in order to optimize clinical interventions.

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1. Introduction

Within the last decade electrical stimulation has been applied to patients with diverse psychiatric diseases, including for treatment resistant major depressive disorder (Schlaepfer et al., 2010; Schlaepfer and Lieb, 2005). There is no general consensual hypothesis concerning the neurocircuitry of depression apart from the "network-model" which suggests that the multiple facets of the syndrome can arise from dysregulation of neuronal activity at numerous loci on the limbic-cortical circuitry (Mayberg, 1997). The lack of a key identified region is reflected in the DBS trials so far: there have been nearly as many targets as studies. A recent clinical trial stimulated the supero-lateral branch of the medial forebrain bundle (slMFB), a structure that projects and interacts with all the previously selected targets: the nucleus accumbens,

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subgenual cingulate cortex, and the ventral capsule/ventral striatum (Anderson et al., 2012; Bewernick et al., 2012; Lozano et al., 2012; Malone et al., 2009). slMFB stimulation, perhaps by modulating all the other previously selected downstream targets, produced rapid and chronic anti-depressive effects at low stimulation intensity (Coenen et al., 2013; Schlaepfer et al., 2013).

The rodent MFB bilaterally stretches from the ventral tegmental area (VTA) in the midbrain to olfactory tubercle in the forebrain, and contains an array of ascending and descending, mostly unmyelinated short nerve fibers. The complexity of this structure is underlined by literature describing around 50 fiber subcomponents and up to 13 different neurotransmitters associated with the MFB (Geeraedts et al., 1990a,b; Nieuwenhuys et al., 1982; Veening et al., 1982). Novel regulatory elements and components of the bundle have been described recently (Bourdy and Barrot, 2012). Due to its position, the MFB has often, but incorrectly been thought of as a synonym for the Lateral Hypothalamic Area (LHA), as large parts of the bundle are imbedded in the LHA. Indeed, neuroanatomical data suggests that many MFB efferent fibers do not passively transit the LHA, but send collaterals and synaptic contacts to this structure before exiting the LHA toward a variety of their target nuclei.

The MFB's intricate relationship with the LHA, and as a substrate of neural transmission between midbrain structures and key basal ganglia and frontal cortical areas, explains why manipulations of the bundle results in diverse motoric and non-motoric impairments. Early electrolytic lesion in the 1950s – destroying indiscriminately both fibers of passage and cell bodies – of the MFB/LHA gave rise to aphagic and adipsic rats which highlighted the LHA'S role in the regulation of food and drink intake (Anand and Brobeck, 1951; Teitelbaum and Epstein, 1962; Teitelbaum and Stellar, 1954). The development of these ideas coincided in time with the rise of intracranial self-stimulation (ICSS) of the MFB that lead to the persisting association of this structure with limbic areas involved in reward, hedonia, motivation, and addiction (Olds and Milner, 1954). The development of more sophisticated neuroanatomical understanding of the MFB in the 60s and 70s, particularly the ability to immunohistochemically map out and selectively lesion the dopaminergic system (Dahlström and Fuxe, 1964; Ungerstedt, 1970), lead to the final "layer" of functions assigned to the bundle, namely motor control, learning and emotional response selection (Björklund and Dunnett, 2007; Schultz, 2013, 2007).

The aim of the current review is to consider the validity of the medial forebrain bundle (MFB) as a stimulation target in psychiatric disorders by examining the neurocircuitry implicated in the disease; furthermore, to examine the early pre-clinical evidence and relevance of ICSS studies to current DBS studies of animal models of psychiatric disorders such as addiction, obsessive–compulsive disorder and depression. The review also considers the viability of bilateral, chronic and continuous high-frequency stimulation of the MFB in rodents, and discusses what areas will need to be addressed in the future to accelerate our neurobiological and mechanistic understanding of this promising neuromodulation strategy.

2. Electrical stimulation of the MFB: intra-cranial self-stimulation (ICSS)

The clinical use of electrical stimulation to map out deep brain structures and guide stereotactic functional operations came into use in the 40s and 50s (Spiegel et al., 1947; Spiegel and Wycis, 1952) with the first stimulation-based therapeutic applications carried out in the 60s (Hassler, 1961; Hassler et al., 1960). The electrical modulation of neural circuit activity in brain structures suspected to play a role in disease pathology lead to the symptomatic treatment using this approach in Parkinson's, Tremor and Dystonia patients starting from the 80s, and to trials in psychiatric disorders over the last decade (Krack et al., 2010; Lozano et al., 2012; Miocinovic et al., 2013; Schlaepfer et al., 2013, 2011). The development of electrical stimulation studies in basic, experimental research took a different path. Over the last sixty years, two principal types of stimulation approaches of the MFB have emerged: the first five decades have been dominated by animal models ICSS; and the last 10 years, the topic of the current review, saw the rise of pre-clinical exploration of DBS.

In the early 50s Olds and Milner observed that a brief electrical pulse delivered into deep brain structures via an electrode increased the likelihood of the rats revisiting the zone that coincided temporally with the stimulus. In a follow-up study animals with electrodes implanted into areas associated with the lateral hypothalamic area were shown to self-administer ad libitum electrical stimulation by lever pressing in a Skinner box (Olds and Milner, 1954). The seminal investigation pointed out structures where self-stimulation had either neutral (caudate nucleus), or aversive behavior effects (medial lemniscus). Crucially, the paper was the first of many to discuss appetitive/reward/motivational behavior in terms of neural substrates in the brain along the MFB axis, particularly in the septum, the cingulate, and tegmentum areas. Indeed, the seminal Olds and Milner experiment opened the way for ICSS-led research into the Lateral Hypothalamic Syndrome, and later on into neurobiology of Addictive Disorders (Koob and Volkow, 2010; Wise, 2002, 1996a, 1996b).

3. MFB and the neurocircuitry of depression

Olds and Milners' ICSS of the MFB – and the studies it spurred – was principally in the context of addiction, but today it is accepted that there are significant overlaps in the neurocircuitry in various psychiatric diseases (Russo and Nestler, 2013). Depression is not a single disease, but a syndrome that covers a multitude of symptoms, and this is mirrored by the different nuclei and their associated neurocircuitry that are thought to be involved. The pathways involved in mood disorders have been the subject of many extensive papers (Nestler et al., 2002a,b; Nestler and Carlezon, 2006; Russo and Nestler, 2013) and is beyond the scope of the current review. The combination of imaging studies, post-mortem methods, and animal models have implicated structures associated with the MFB in depression such as the nucleus accumbens (NAC), the cingulate gyrus, the septum, the hippocampus, the amygdala, the pallidum, the medial thalamus, the hypothalamus, the VTA, the lateral habenula, or the periaqueductal gray (Price and Drevets, 2012). While focus in the past has been on aspects of the prefrontal cortex and the hippocampus, the pathways within the MFB connecting the VTA with the NAC, the mesolimbic dopaminergic (DA), and the VTA with the pre-frontal cortex, the mesocortical DA projection, have emerged as central substrates in the etiology of several psychiatric diseases, including depression.

Anhedonia, the reduction of reward sensation or pleasure, a typical symptom in clinical depression as well as in the animal models used, is thought to be rooted in the deregulation of the VTA to NAC pathway (Russo and Nestler, 2013). Clinical data backs this up showing reduced activity in the NAC in depressed patients (Mayberg et al., 2000), as do certain animal models, for example the Flinders Sensitive Line (FSL) rats that have been selectively breed to express depression-like phenotypes (Friedman et al., 2005; Neumann et al., 2011). The VTA is a heterogeneous structure containing GABAergic and Glutaminergic neurons, but its the DAergic projections, making up around 60% of the efferents, whose phasic firing encode the reward signal at the level of the NAC (Dobi et al., 2010; Russo and Nestler, 2013; Schultz, 2013).

The MFB, in particular the mesolimbic and the mesocortical DAergic pathways that pass through the bundle, is also considered to be the neural substrate for the so called SEEKING system, one