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Deep Brain Stimulation for the Treatment of Addiction: Basic and Clinical Studies and Potential Mechanisms of Action

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Abstract

Rationale—Deep brain stimulation (DBS) has achieved substantial success as a treatment for movement disorders such as Parkinson’s disease. The therapeutic efficacy and relative lack of serious side effects resulted in the expansion of DBS into the treatment of many other diseases, including obsessive-compulsive disorder, Tourette’s and depression, among others. More recently, a limited number of basic and clinical studies indicated that DBS may also be useful in the treatment of various addictions.

Objectives—Here, we briefly summarize the history of DBS and review the basic and clinical studies focused on DBS and addiction. We also examine the potential mechanisms that may underlie the effects of DBS.

Results and Conclusions—The available data indicate that DBS is a promising therapeutic modality for the treatment of addiction. Thus far, the nucleus accumbens and subthalamic nucleus are the most promising sites for DBS reversing aspects of addiction. The mechanisms underlying DBS are complex and likely vary from region to region. Emerging evidence indicates that DBS of the nucleus accumbens produces its effects, at least in part, by antidromic activation of cortico-accumbal afferents that stimulate inhibitory mPFC interneurons via recurrent collaterals.

The origins of deep brain stimulation are linked to the rise and fall of psychosurgery. Lobotomy for the treatment of psychiatric disorders peaked in popularity around 1949 when its pioneer, Egas Moniz, was awarded the Nobel Prize. The development of antipsychotic drugs in the 1950s coupled with the indiscriminant and reckless application of psychosurgery for psychiatric diseases severely diminished the reputation of therapeutic lesions (El-Hai 2005; Valenstein 1986). Although reining in perversions such as the transorbital (i.e. “ice pick”) lobotomy was imperative, it was unfortunate that promising procedures such as stereotaxic pallidotomy and thalamotomy for movement disorders also fell out of fashion (Lozano and Lipsman 2013; Sventnilson et al. 1960).

Therapeutic stimulation of the brain was originally developed in the 1950s in order to produce “reversible lesions” (Lozano and Lipsman 2013) and was applied to various disorders, notably psychosis and chronic intractable pain (Croft 1952; Delgado et al. 1952; Mazars 1975). DBS proved to be of limited utility and given that there were effective pharmacotherapies for these disorders DBS did not gain widespread acceptance. By the 1980s it was becoming clear that pharmacological treatments for Parkinson’s disease (PD) such as levodopa not only did nothing to halt the progression of the disease but also

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produced significant and sometimes disabling side effects of their own (Benabid et al. 2001). At this time, therapeutic lesions were reintroduced as PD therapies and gained popularity for this purpose into the 1990s (Hariz 2012; Laitinen et al. 1992). In the 1980s, Benabid and colleagues resurrected DBS and applied it to movement disorders. They reported that high-frequency stimulation of the thalamus relieved tremors in Parkinson's patients in a manner similar to thalamic lesions (Benabid et al. 1987; Lozano and Lipsman 2013). This study marked the onset of the modern era of DBS therapies (Benabid et al. 1987).

In 1990, pre-clinical research indicated that the subthalamic nucleus (STN) was an additional target for both lesion and DBS therapies for PD (Bergman et al. 1990). Benabid and colleagues were the first to test STN DBS for the treatment of advanced PD (Limousin et al. 1998; Limousin et al. 1995). Their results indicated that STN DBS for PD was so effective that pharmacotherapies could be reduced or eliminated (Limousin et al. 1998; Limousin et al. 1995). STN lesions also were shown to be effective in the treatment of PD but produced more unwanted side effects than DBS (Limousin et al. 1998). DBS had the further advantage of being reversible (i.e. DBS can be stopped immediately if negative side effects emerge) and malleable in that the stimulation parameters can be modified to maintain therapeutic effects. DBS also is unburdened by the unfortunate history of therapeutic lesions. For these reasons, DBS has steadily grown in popularity over the past quarter century (Hariz 2012) and was approved by the U.S. Food and Drug administration for the treatment of essential tremor (in 1997), Parkinson's disease (in 2002) and dystonia (in 2003).

DBS for the treatment of psychiatric disorders

Somewhat surprisingly given the risks associated with neurosurgery, the therapeutic use of DBS for psychiatric disorders progressed rapidly. The symptoms of Tourette's syndrome and obsessive compulsive disorder (OCD) were reduced following DBS of the thalamus and internal capsules, respectively (Nuttin et al. 1999; Vandewalle et al. 1999). The rationale for these studies was based on prior lesion studies (Hariz 2012). More recently, results of imaging studies were used to justify DBS of the subgenual cingulate for refractory depression (Mayberg et al. 2005). The rapid expansion of the disorders deemed suitable for DBS, which now range from dementia to urinary incontinence (Lozano and Lipsman 2013), is due to the view that DBS is relatively safe. Although serious adverse events such as hemorrhage occur in less than 2% of DBS patients, the surgery is fatal up to 0.4% of the time (Hamani et al. 2008; Voges et al. 2006). Although these numbers may initially seem unacceptably high, one has to bear in mind the severity of most the diseases in question including addiction, which often is associated with high rates of relapse. Given the high costs associated with severe, treatment-resistant addiction, many have concluded that continuing research on DBS as an addiction therapeutic is worth the risks (Muller et al. 2012), although this opinion is not universally embraced (Carter and Hall 2011).

DBS for the treatment of addiction

The use of DBS for the treatment of addiction was serendipitous. Some PD patients escalate their intake of dopamine replacement therapeutics in a manner similar in some ways to addiction, a phenomenon known as dopamine dysregulation syndrome (Lawrence et al. 2003). It was reported that STN DBS for the treatment of PD in two patients alleviated the symptoms of PD and also the desire to misuse PD pharmacotherapies. In fact, therapeutic levodopa administration was greatly reduced in one patient and eliminated in the other with no adverse effects (Witjas et al. 2005). Resolution of dopamine dysregulation syndrome following STN DBS for PD was subsequently confirmed (Eusebio et al. 2013; Knobel et al. 2008; Lhommee et al. 2012), although this effect was not observed in all patients (Lim et al.

2009). These results coupled with previous work indicating that repeated cocaine decreased STN metabolic activity (Uslaner et al. 2003) and, importantly, that lesions of the STN decrease motivation to take cocaine in rats (Baunez et al. 2005) suggested that STN DBS might represent a therapeutic for addiction. A recent preclinical study in rats indicated that STN DBS reduced both cocaine taking and cocaine seeking (Rouaud et al. 2010). Another clinical case study in 2007 focused on nucleus accumbens DBS in a patient with agoraphobia and panic attacks (Kuhn et al. 2007). The patient also was a heavy drinker, averaging over 10 alcoholic beverages per day. Although accumbens DBS had only a slight influence on the patient's anxiety disorder, his alcohol intake was rapidly and dramatically reduced. In fact, a month after stimulation the patient reported little desire to consume alcohol and alcohol-free days prevailed (Kuhn et al. 2007). Similarly, three additional patients receiving accumbens DBS for other indications were reported to spontaneously quit smoking (Kuhn et al. 2009).

At this same time pre-clinical experiments were progressing specifically focusing on the use of DBS to modulate aspects of drug taking and seeking. Most basic studies in this area have focused on the nucleus accumbens, the ventral portion of the striatum that processes limbic information and is critically involved in the reinforcing effects of drugs of abuse (Pierce and Kumaresan 2006). DBS of the rat nucleus accumbens prevented morphine conditioned place preference (Liu et al. 2008), attenuated cocaine priming-induced reinstatement of drug seeking (Vassoler et al. 2008) and decreased alcohol preference and/or intake in rats (Henderson et al. 2010; Knapp et al. 2009).

The nucleus accumbens is divided into two major subregions, the core and shell, which are differentiated both functionally and anatomically. For example, the anterior cingulate and dorsal prelimbic cortices preferentially innervate the core, while the infralimbic and ventral prelimbic cortices project to the shell (Heimer et al. 1997; Zahm 2000). DBS applied to either the accumbens core or shell reduced alcohol consumption (Knapp et al. 2009). In contrast, DBS of the medial accumbens shell, but not the accumbens core, attenuated cocaine priming-induced reinstatement of drug seeking (Vassoler et al. 2010; Vassoler et al. 2008). DBS of the dorsal striatum also had no effect on the cocaine seeking, which further shows that the effects of DBS are highly region-specific. Therefore, more precise targeting of the nucleus accumbens shell may improve the efficacy of DBS for the treatment of some addictions. Importantly, accumbens shell and STN DBS had no effect on sucrose seeking indicating that DBS produced reinforcer-specific effects (Rouaud et al. 2010; Vassoler et al. 2008).

More recent clinical studies have assessed the safety and efficacy of nucleus accumbens DBS as a drug addiction therapeutic (Muller et al. 2012). A case study revealed complete remission of heroin abuse by one male for over 6 years. Remarkably, after 2.5 years the stimulation was turned off and the patient remained abstinent (Zhou et al. 2011). A similar case report indicated that DBS of the nucleus accumbens resulted in prolonged cessation of heroin use, with the exception of a 2-week period of relapse (Valencia-Alfonso et al. 2012). Another case study reported that DBS of the nucleus accumbens produced marked improvement in symptoms of OCD, the therapeutic target, and also resulted in unintended and "effortless" smoking cessation and weight loss (Mantione et al. 2010). In all cases, accumbens DBS produced no unwanted side effects. Indeed, DBS of the nucleus accumbens was reported to have beneficial effects on tests of attention, learning and memory, executive function and visual perception in humans (Grubert et al. 2011).

DBS mechanism of action

Surprisingly, the mechanism of action of DBS that is responsible for its therapeutic effects remains unclear. Recent work from our laboratory has tried to unravel the potential mechanisms that may underlie the ability of accumbens shell DBS to attenuate the reinstatement of cocaine seeking. There is evidence that DBS increases neuronal activity within the stimulated nucleus (McIntyre et al. 2004; Montgomery and Gale 2008) and we showed that DBS of the accumbens shell or core increased c-Fos immunoreactivity, a measure of neuronal activation, in these nuclei (Vassoler et al. 2010). As noted above, DBS of the shell but not the core attenuated cocaine reinstatement. Moreover, since enhancing neuronal activity in the nucleus accumbens actually promotes the reinstatement of cocaine seeking (Cornish et al. 1999; Ping et al. 2008), it seems unlikely that DBS-induced activation of the nucleus accumbens shell is responsible for the attenuation of cocaine reinstatement.

It also has been suggested that DBS inhibits the stimulated nucleus via depolarization inactivation and/or activation of inhibitory neurons (Benazzouz and Hallett 2000; Boraud et al. 1996; Kiss et al. 2002). In order to examine this possibility, we administered a cocktail of GABA agonists or lidocaine into the core or shell of the nucleus accumbens. Microinjection of the GABA agonists or lidocaine into the core, but not the shell, attenuated cocaine reinstatement (Vassoler et al. 2010), which suggested that the effect of shell DBS on cocaine reinstatement was not due to local inactivation. Moreover, the lack of a lidocaine effect in the shell suggested that the influence of shell DBS on cocaine reinstatement was not due to impaired neuronal transmission in axons of passage.

It is becoming clear that the effects of DBS are more complex than simple local excitation or inhibition. Indeed, DBS was shown to preferentially stimulate axons terminals (Nowak and Bullier 1998) resulting in broader, circuit-wide influences (Ewing and Grace 2013; Gradinaru et al. 2009; McCracken and Grace 2007; Vitek 2002; Windels et al. 2000). Consistent with these findings, electrophysiological studies showed that accumbens DBS attenuated the spontaneous activity of cortico-accumbal glutamatergic neurons but also stimulated cortical interneurons, apparently via recurrent inhibition (McCracken and Grace 2007; 2009). In fact, prolonged accumbens DBS appeared to produce long-term potentiation in cortical interneurons thereby contributing to the sustained action of DBS (McCracken and Grace, 2007). Similarly, the results of our c-Fos study indicated that DBS of the accumbens shell activated the infralimbic cortex, which could have contributed to the DBS-induced activation of the shell (Vassoler et al. 2010). However, GABA agonist-induced inactivation of the infralimbic cortex attenuated the reinstatement of cocaine seeking induced by a priming injection of cocaine (Vassoler et al. 2010), which is consistent with accumbens DBS indirectly activating GABAergic interneurons (see Figure 1). Taken together, these results suggested that DBS of the accumbens shell produced complex effects throughout the circuit in which the shell is embedded. It is generally agreed that cocaine self-administration results in aberrant activity in the cortico-accumbal system (Kalivas et al. 2005; Schmidt and Pierce 2010) and it appears that normalization of this system is one of the main effects of accumbens DBS. It should be emphasized that these mechanisms may be specific to the nucleus accumbens/striatum. That is, it is likely that local and circuit-wide influences of DBS will depend on the stimulated structure and its specific afferents, efferents, cell types, ratio of projection neurons to interneurons, transmitter systems, etc.

Conclusions

DBS is being assessed for utility in an ever-widening array of neurological and psychiatric diseases including addiction. Recent basic and clinical studies indicate that DBS of the

nucleus accumbens substantially reduces drug intake and craving, which highlights the promise of this therapeutic modality in the treatment of intractable addiction. However, significant ethical issues remain and clinicians should be particularly vigilant in explaining the risk of DBS to drug dependent patients, who are likely to be much younger than individuals seeking treatment for neurodegenerative diseases (Muller et al. 2012). Thus far the nucleus accumbens is the most promising target in that accumbens DBS was shown to be effective when tested with multiple classes of abused drugs and was relatively free of unwanted side effects. However, other targets should continue to be examined as well, including the mPFC and STN (Luigjes et al. 2012). Finally, research into the mechanisms through which DBS influences drug intake and craving are critically important and may reveal modulation of neurotransmitters and neuronal circuits not typically associated with addiction, which could lead to novel pharmacotherapeutic targets.

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Figure 1.

Cartoon depicting a mechanism whereby DBS of nucleus accumbens (NAc) influences neuronal activity in the medial prefrontal cortex (mPFC). It is proposed that DBS of the NAc (1) produces antidromic activation of cortico-accumbal afferents (2) that stimulates mPFC interneurons via recurrent collaterals (3). DBS-induced activation of mPFC GABAergic interneurons (neuron with black circle cell body), in turn, inhibits cortical pyramidal neurons (neuron with triangular cell body). Modified from McCracken and Grace, 2007.