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Chronic Unilateral Stimulation of the Nucleus Accumbens at High or Low Frequencies Attenuates Relapse to Cocaine Seeking in an Animal Model

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ABSTRACT

Background: Deep brain stimulation (DBS), a form of neurosurgical intervention that is used to modulate the electrophysiological activity of specific brain areas, has emerged as a form of therapy for severe cases of treatment-refractory addiction.
Objective/Hypothesis: Recent research suggests that the nucleus accumbens (NAC) is a promising target area for DBS in addiction. The current experiments were designed to determine optimal parameters of stimulation and long-term efficacy of NAC DBS in an animal model of cocaine addiction.
Methods: Rats were implanted with a stimulating electrode in the right NAC and exposed to chronic cocaine self-administration (0.5 mg/kg/infusion). Rats underwent drug seeking tests by exposing them to the self-administration context paired with cocaine challenge (5 mg/kg i.p.) on days 1, 15 and 30 after withdrawal from cocaine self-administration. Low-frequency (LF, 20 Hz) or high-frequency (HF, 160 Hz) DBS was applied for 30 min daily for 14 consecutive days starting one day after drug withdrawal.
Results: Rats exhibited robust drug-seeking 1, 15 and 30 days after withdrawal from cocaine self-administration, with responding being highest on day 15. Both LF and HF attenuated cocaine seeking on day 15 post-withdrawal by 36 and 48%, respectively. Both forms of stimulation were ineffective on the tests conducted on days 1 and 30.
Conclusion: The present data showed that unilateral DBS of the NAC effectively attenuated cocaine relapse after 15 days of drug withdrawal, with therapeutic-like effects seemingly diminishing after DBS discontinuation. This evidence provides support for DBS as a promising intervention in intractable cases of stimulant addiction.

Introduction

Deep brain stimulation (DBS) is a neurosurgical intervention in which implanted electrodes deliver microelectrical pulses to target areas in the brain. DBS has several functional advantages and safety features compared with neurosurgical ablation. DBS is less invasive, reversible and adjustable (e.g., current amplitude or frequency). DBS of thalamic and subthalamic nuclei and other brain regions has emerged in recent times as a clinically effective treatment strategy for a number of neuropsychiatric patients who fail to respond to standard pharmacological or behavioral therapies, including those afflicted by Parkinson's disease (PD) [1–3], dystonia and tremor [4], obsessive-compulsive disorder (OCD) [5], Tourette's syndrome [6], and major depression [7,8] (For review: [9]).

DBS has also been proposed for patients suffering from treatment-refractory addiction to drugs. Drug addiction is a chronically relapsing disorder characterized by an overwhelming desire to seek and take drugs, loss of control in limiting intake and, when access to the drug is inhibited, emergence of a negative emotional state [10]. However, it is not yet entirely clear which

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brain areas should be targeted for DBS to produce effective remission of symptoms and protection against relapse (For review: [11]). The nucleus accumbens (NAC) is involved in mediating the rewarding and reinforcing properties of drugs of abuse [12]. Moreover, the NAC seems to play an important role both in craving [10] and in the transition from voluntary to compulsive drug use [10,13,14]. Several studies offer support for the NAC as a promising candidate for DBS treatment in addiction [11], as well as related disorders such as obsessive-compulsive disorder [15].

Relapse is one of the most insidious and difficult symptoms to treat in drug addiction. It has been previously reported that NAC DBS attenuated cocaine priming-induced reinstatement of cocaine seeking [16]. In this study, however, DBS was applied during the reinstatement session only, thus leaving the question open as to whether the effects of DBS are task-specific (i.e., cocaine-induced reinstatement), or may instead be more general and long lasting. There is only one previous publication describing the effects of NAC DBS on drug seeking after the stimulation was turned off. Guo and colleagues (2013) showed decreased cue- and heroin-induced reinstatement following DBS exposure administered prior to the extinction sessions, which were conducted over seven consecutive days [17], thus suggesting that repeated NAC DBS may have therapeutic effects that extend beyond the period of stimulation.

Although the mechanisms underlying the effects of DBS treatment are largely unknown, there is agreement that the effects of DBS are not achieved simply by direct actions on the neurons located near the electrode site. Circuit-level modulation may also be important, achieved primarily through antidromic stimulation of afferent cortical projections and/or through activation of basal ganglia thalamocortical loop pathways. Recently, Vassoler and colleagues (2013) reported evidence that stimulation of the NAC shell attenuated drug reinstatement through GABAergic interneuron activation in the prefrontal cortex, resulting from antidromic stimulation of cortico-accumbal afferents [18]. Prolonged accumbens stimulation has been previously shown to produce long-term potentiation in cortical interneurons, potentially contributing to the long-term effects of DBS [19,20].

If the effects of NAC DBS on relapse to drug seeking are mainly mediated by network interactions then it may be possible to disrupt the behavior at different stimulation frequencies. In the current study, we aimed to investigate the potential therapeutic application of varying levels of stimulation applied to the NAC, namely high-frequency (HF) DBS or low-frequency (LF) DBS, in a drug self-administration (S-A) model of cocaine addiction. These parameters have not been previously compared in the same model. In addition, we aimed to study the temporal parameters of the relapse response when combined with DBS therapy and evaluate the long-term efficacy of the treatment. We used unilateral stimulation in order to reduce the potential complications of surgical implantation. Although it is common practice and positive results have been gained, bilateral implantations lead to greater clinical complications such as post-operative confusion, speech difficulties and cognitive dysfunction [21]. Moreover, previous studies have shown that unilateral and bilateral stimulation of the NAC can also be effective at reducing heroin seeking behaviors [17].

Materials and methods

Subjects

Male 10–12 week-old Long-Evans rats ($n = 40$) were obtained from the University of Canterbury animal facility. Animals were individually housed and kept on a 12 h light/dark cycle with moderate food restriction (20 g/day) [22,23] and water available *ad libitum*. All procedures were carried out in accordance with the NIH Guide for the Care and Used of Laboratory Animals, and approved by the Animal Ethics Committee of the University of Canterbury (2012/35R).

Apparatuses

Operant S-A chambers (Panlab S.L., Barcelona, Spain) enclosed within sound-attenuating chambers were used to train and test the animals for cocaine and saccharin S-A and relapse. The chambers were fitted with two response levers, serving as the active (right) and inactive (left) levers. An active lever response resulted in delivery of a drug or saline reinforcer dispensed from a pump located outside of the attenuation chamber and the activation of a stimulus light located directly above the active lever. An inactive lever response was programmed to have no consequences. The chambers were equipped with a house light located in the attenuation chamber.

DBS procedures were conducted in operant chambers (Med Associates, VT, USA) enclosed in sound-attenuating boxes. These chambers were visually different to the S-A chambers and had the opposite orientation to reduce the possibility of inducing extinction responses or interference with the S-A procedures. The DBS chambers were fitted with a general house light and a swivel connected to the external dual channel stimulator (Grass Technology, Model S88, RI, USA), the voltmeter and the oscilloscope to measure the frequency and amplitude of the stimulation. The house light, positioned directly in the center of the right wall, was illuminated throughout the session. The leads in the swivel connected to the electrode that had been previously implanted in the rat. An oscilloscope was used to ensure that the biphasic pulses generated through the stimulator were effectively delivered to the brain.

Surgery

Surgical procedures for catheter implantation were as described previously [22,24,25]. Before surgery, animals were anaesthetized with i.p. injections of ketamine (Ketolar®, 85 mg/kg) and medetomidine (Domitor®, 0.35 mg/kg). Catheters (Camcaths, UK) were implanted into the right jugular vein exiting dorsally in between the scapulae and sutured in place. Following catheter implantation, rats were mounted in a stereotaxic apparatus in order to implant bipolar, two channel stainless steel electrodes (Plastics One, USA) unilaterally into the NAC [17,26,27] according to the following coordinates relative to bregma: AP +1.3 mm, ML −1.4 mm, DV −7.1 mm from brain surface. Electrodes were secured in place with stainless steel mounting screws (Plastics One, USA) and dental acrylic. Electrodes were implanted into the right NAC, as in previous studies [17]. It has been previously reported that relative metabolic changes in the right insular region, right orbitofrontal cortex and right striatum correlate with cocaine craving in humans [28–31] and that neurophysiological activity displays right-sided asymmetry in opioid addicts [32]. All animals, including sham stimulated rats, were exposed to the same surgical procedures. Animals were allowed 7 days recovery before experiments began.

Pharmacological treatments

Cocaine HCl (National Institute of Drug Abuse, NIH, USA) was used for the S-A experiment. Cocaine was delivered to the animals intravenously, with each infusion administering 0.5 mg/kg. Cocaine was dissolved in 0.9% saline at a volume of 1.33 mg/ml. For the relapse tests cocaine was administered at a dose of 5 mg/kg i.p.