Experimental Neurology 225 (2010) 302–309

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Deep brain stimulation of the nucleus accumbens shell increases impulsive behavior and tissue levels of dopamine and serotonin

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ARTICLE INFO

Article history:
Received 20 April 2010
Revised 8 June 2010
Accepted 29 June 2010
Available online 11 July 2010

Keywords:
Nucleus accumbens
High frequency stimulation
Impulsive behavior
Dopamine
Serotonin

ABSTRACT

The nucleus accumbens (NAc) is gaining interest as a target for deep brain stimulation (DBS) in refractory neuropsychiatric disorders with impulsivity as core symptom. The nucleus accumbens is composed of two subterritories, core and shell, which have different anatomical connections. In animal models, it has been shown that DBS of the NAc changes impulsive action. Here, we tested the hypothesis that a change in impulsive action by DBS of the NAc is associated with changes in dopamine levels. Rats received stimulating electrodes either in the NAc core or shell, and underwent behavioral testing in a reaction time task. In addition, in a second experiment, the effect of DBS of the NAc core and shell on extracellular dopamine and serotonin levels was assessed in the NAc and medial prefrontal cortex. Control subjects received sham surgery. We have found that DBS of the NAc shell stimulation induced more impulsive action but less perseverative checking. These effects were associated with increased levels of dopamine and serotonin in the NAc, but not in the medial prefrontal cortex. DBS of the NAc core had no effect on impulsive action, but decreased perseverative responses indicative of a better impulse control. In these subjects, no effects were found on neurotransmitter levels. Our data point out that DBS of the NAc shell has negative effects on impulsive action which is accompanied by increases of dopamine and serotonin levels in the NAc, whereas DBS of the NAc core has beneficial behavioral effects.

Introduction

Deep brain stimulation (DBS) is nowadays a widely applied therapy for intractable neurological disorders and the application is moving towards psychiatric disorders (Awan et al.; 2009; Hardesty and Sackeim, 2007; Schläpfer and Bewernick, 2009). In this respect, the nucleus accumbens (NAc, main component of the ventral striatum) is a popular target for DBS, since its dysfunction is held responsible for (some) of the key symptoms of several major psychiatric disorders including obsessive compulsive disorder (Abelson et al., 2005; Aouizerate et al., 2004; Kuhn et al., 2007; Okun et al., 2007; Sturm et al., 2003), Tourette's syndrome (Visser-Vandewalle 2007; Visser-Vandewalle et al., 2006) and major depression (Schlaepfer et al., 2008). The mechanisms underlying the therapeutic effects of DBS are multifaceted (Benabid, 2007; Gubellini et al., 2009; McIntyre et al., 2004a, 2004b), and depend on the brain region stimulated (Kringelbach et al., 2007). In the case of DBS of the NAc, recent evidence suggests an antidromic inhibition of orbitofrontal cortex activity and an enhanced thalamo-cortical synchronicity (McCracken and Grace, 2007, 2009).

Anatomically, the NAc is divided into a medio-rostrally located shell and a latero-caudally located core (Jongen-Relo et al., 1994; Voorn et al., 1989; Zaborszky et al., 1985; Zahm and Brog, 1992). There is a rich interplay between the dopaminergic and serotonergic system in the NAc. The dopaminergic input comes from the ventral tegmental area (VTA) and the medial part of the substantia nigra pars compacta (SNc), and the serotonergic input comes mainly from the dorsal raphe nucleus. Cortical inputs of the NAc originate mainly in the medial orbitofrontal, anterior cingulate and medial prefrontal cortices (mPFC) (Ferry et al., 2000; Groenewegen et al., 1996, 1999; Kunishio and Haber, 1994; Zahm and Brog, 1992). The mPFC projects topographically to the NAc. The dorsal part innervates the core while the ventral part sends fibers to the shell (Berendse et al., 1992; Brog et al., 1993). In turn, the NAc core

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doi:10.1016/j.expneurol.2010.06.022

projects to the subcommissural part of the ventral pallidum (VP), which is reciprocally connected with the subthalamic nucleus, and the entopeduncular nucleus. The core follows the classical pattern of striatal connectivity (Groenewegen and Berendse, 1990; Groenewegen and Russchen, 1984; Groenewegen et al., 1999). The NAc shell efferent fibers reach the ventral and medial parts of the VP, but also the VTA and SNc (Groenewegen et al., 1993). Thus, the shell projections richly innervate the main dopaminergic nuclei (Belin and Everitt, 2008; Groenewegen et al., 2003; Haber et al., 2000; Nauta et al., 1978). These differences in connectivity between the NAc core and shell are also apparent at the behavioural level, such as set shifting (Floresco et al., 2006), feeding behaviour (Maldonado-Irizarry et al., 1995), appetitive Pavlovian approach, instrumental conditioning, latent inhibition or prepulse inhibition (Pothuizen et al., 2005a, 2005b; Weiner et al., 1996), drug seeking (Ito et al., 2004), mediation of amphetamine effects (Cole and Robbins, 1989; Murphy et al., 2008; Parkinson et al., 1999; Pattij et al., 2006; Weiner et al., 1996) and impulsive behaviour (Murphy et al., 2008; Pothuizen et al., 2005a; Sesia et al., 2008).

Since it is still unclear which part of the NAc should be used for DBS, in a previous experiment we have investigated the effects of NAc core and shell DBS in a rat model and found a differential effect of high frequency stimulation (Sesia et al., 2008). Stimulation of the NAc shell induced more premature responses while DBS of the NAc core produced the opposite effect. The neurochemical consequences of NAc stimulation are not known. A change in premature responding was attributed to a change in the DA system (Cole and Robbins, 1987, 1989; Harrison et al., 1997). Serotonin (Evenden, 1999; Winstanley et al., 2004a, 2004b) and its interactions with the DA system (Winstanley et al., 2003, 2005) have been shown to mediate impulsivity as well. Here, we predicted that changes in impulsive action elicited by DBS of the NAc would be associated with changes in 5-HT and DA levels. This was based on evidence showing that higher levels of 5-HT in the medial prefrontal cortex (mPFC) were correlated with increased premature responding (Dalley et al., 2002; Puumala and Sirvio, 1998), and that increased DA activity was consistently found to increase premature responding (Blokland et al., 2005; Cole and Robbins, 1987; Pezze et al., 2006). We performed DBS of the NAc core and shell and evaluated the effects on impulsive action using the reaction time (RT) task. In addition, extracellular DA and 5-HT levels were assessed in the NAc and mPFC using high pressure liquid chromatography in rats.

Materials and methods

Subjects

Male Lewis rats were used for the experiment (12 weeks old, bred and housed at the Central Animal Facility of Maastricht University, Maastricht, The Netherlands). The rats were housed in standard transparent polypropylene cages on sawdust bedding in an air-ventilated room under a 12/12-h reversed light/dark cycle with controlled room temperature and humidity 60–70%. The rats had free access to food and water. During testing rats were given 12–15 g of standard laboratory chew (Hope Farms, Woerden, The Netherlands) per day, thereby reducing their body weight to 90 % of their *ad libitum* weight. The animal experiments and ethics committee of Maastricht University gave approval for the experiments. This study consisted of two experiments, one behavioral and one neurochemical. For both experiments four groups of rats were used:

Experiment 1 (behavioural experiment)	Experiment 2 (neurochemical)
1) NAc core DBS group ($N=10$)	1) NAc core DBS group ($N=7$)
2) NAc core sham group ($N=7$)	2) NAc core sham group ($N=4$)
3) NAc shell DBS group ($N=10$)	3) NAc shell DBS group ($N=7$)
4) NAc shell sham group ($N=7$)	4) NAc shell sham group ($N=4$)

Behavioural procedure

Reaction time task

In the first experiment, the animals were trained to perform a RT task. The performances of the rats were tested in operant chambers as described earlier (Blokland, 1998; Sesia et al., 2008). After 20 days of training, the rats were tested for RT performance. The task is as follows. A trial starts when the light of the magazine panel, which is located in the center of the front wall of the Skinner box, is turned on. The hinged panel has to be kept pressed until a tone is presented; a high tone (10 kHz, 80 dB) precedes the insertion of the left lever, whereas a low tone (2.5 kHz, 80 dB) precedes the insertion of the right lever. A variable period between the pushing of the hinged panel and the onset of the tone (hold duration) was set at 0.5 s. On the presentation of the sound, a lever is inserted either on the right or on the left side of the magazine and a light on the top of the lever is switched on; both of the levers are equidistant to the food magazine. The rat has to press the cued lever in order to obtain a food pellet. When the rat removes its nose from the magazine before the end of the hold duration (so-called premature responding) the trial is reinitialized. An inter-trial time (10 s) was applied. The session lasted until 60 trials were completed or when test duration reached 30 min.

Behavioural parameters

The following parameters were used to assess the performance during testing. Motor time (MT), is the mean latency between the release of the panel and the lever press. MTs longer than 2 seconds are assumed not to reflect true motor time (Blokland, 1998). The reaction time (RT) is the mean latency between the onset of the tone and the release of the panel. RTs below 100 ms or longer than 1500 ms were disregarded (Cao et al., 2006).

Premature responding ratio (PR) is the number of premature responses divided by the number of successful trials; it may also be referred as impulsive action, an increase of this parameter is considered as an increase in motor impulsivity (Blokland, 1998). Intertrial responses (ITR) were also recorded; higher score may be seen as failure to inhibit the instrumental response (Winstanley et al., 2006).

Additionally we measured the overall duration of a session (session time, ST). As described in earlier work (Sesia et al., 2008), the rat has little control over initiating the next trial; we calculated the specific reengagement time (SRT) which was defined as the mean time elapsed between the onset of the magazine light (i.e. start of trial) and a nose poke. If the animal started the trial already in the magazine, this value (e.g. 0 s) was discarded (Sesia et al., 2008).

Surgical procedure

After obtaining the preoperative behavioural parameters (i.e. no change in behavioural parameters on 3 successive sessions) the rats underwent surgery. The surgical technique has been described in more detail previously (Temel et al., 2005, 2007). Animals were anesthetized with isoflurane and were placed in a stereotactic apparatus (Stoelting, USA; model 51653). Two burr holes were made in the skull immediately above the targets to allow for insertion of the electrodes. The stereotactic coordinates were, from Bregma, for the NAc shell (AP = 1.2 mm, ML = ±0.7 mm, V = −7.4 mm) and for the NAc core (AP = 1.2 mm, ML = ±1.5 mm, V = −7.4 mm). A construction of two stimulating electrodes (Technomed, The Netherlands), both concentric and bipolar, with a tip diameter of 50 μm and a shaft diameter of 250 μm, was employed in this experiment (Temel et al., 2005, 2007). The electrodes were fixed in position using dental cement (Heraeus Kulzer, Hanau, Germany).