

## RAPID REPORT

# DEEP BRAIN STIMULATION OF THE POSTERIOR HYPOTHALAMIC NUCLEUS REVERSES AKINESIA IN BILATERALLY 6-HYDROXYDOPAMINE—LESIONED RATS

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**Abstract**—Deep brain stimulation (DBS) of the basal ganglia motor circuitry is a highly effective treatment for the debilitating motor symptoms of Parkinson's disease (PD). However, recent findings have indicated promising potential for PD therapy with DBS in brain structures outside the basal ganglia. For example, high frequency stimulation of the posterior hypothalamic nucleus (PH) can reverse haloperidol-induced akinesia in rats [Jackson J, Young CK, Hu B, Bland BH (2008) High frequency stimulation of the posterior hypothalamic nucleus restores movement and reinstates hippocampal-striatal theta coherence following haloperidol-induced catalepsy. *Exp Neurol* 213:210–219]. In the current study, we used the bilateral 6-hydroxydopamine lesion model of Parkinsonian akinesia in male Long-Evans rats to further explore the efficacy of PH DBS. The application of PH DBS in lesioned animals reversed akinesia in an active avoidance paradigm with increased latency compared to pre-lesion performance. The dramatic reversal of akinesia in two models of rodent Parkinsonism by PH DBS warrants further exploration of its therapeutic potential. Crown Copyright © 2009 Published by Elsevier Ltd on behalf of IBRO. All rights reserved.

**Key words:** medial forebrain bundle, high frequency stimulation, active avoidance, Parkinson's disease, bradykinesia, haloperidol.

The subthalamic nucleus (STN) is the most common site for deep brain stimulation (DBS) in patients with Parkinson's disease (PD; for a recent review, see Benabid et al., 2009). Although STN DBS decreases tremor and rigidity (Krack et al., 2003), other symptoms such as gait disruption with freezing are less responsive, leading to the assessment of new targets such as the pedunculopontine tegmental nucleus (PPT) for both postural and gait disturbances in primates and humans (Jenkinson et al., 2004; Plaha and Gill, 2005; Stefani et al., 2007; Nandi et al., 2008). Stimu-

lation of the posterior hypothalamic nucleus (PH) induces a repertoire of non-stereotypical, naturalistic movements (Bland and Vanderwolf, 1972; Slawinska and Kasicki, 1995; Jackson et al., 2008; Bland, 2009) in behaving animals. We have recently reported that in animals made akinetic by systemic haloperidol, PH DBS was able to quantitatively restore exploratory behavior in an open field setting, reduce latency to fall in a catalepsy grip test, and reinstate the ability to perform learned avoidance (Jackson et al., 2008). To further examine the therapeutic potential of PH stimulation in the treatment of parkinsonian akinesia, we used bilateral medial forebrain bundle (mfb) 6-hydroxydopamine (6-OHDA) lesion to induce severe akinesia (Jolicœur et al., 1991; Hayakawa et al., 1999). The active avoidance paradigm utilized in the PH DBS haloperidol study (Jackson et al., 2008) was used in the current study to allow a direct comparison of the two parkinsonian models. We report that PH DBS was able to reverse 6-OHDA-induced akinesia, reinforcing its potential for clinical application.

## EXPERIMENTAL PROCEDURES

Singly housed male Long-Evans rats ( $n=15$ , 300–450 g) obtained from the Animal Care Facility at the University of Calgary were given food and water *ad libitum*. All aspects of experimentation followed the Canadian Council for Animal Care guidelines. Under ketamine/xylazine (100 mg/kg i.m., 85:15 mix, Wyeth, Guelph, ON, Canada) anesthesia, twisted bipolar electrodes (MS303, Plastics One, Roanoke, VA, USA) were inserted in the dorsal part of the PH (AP  $-3.8$ , ML  $-0.2$ , DV  $-7.6$ , 0.5 mm tip separation). Two additional pairs of bipolar recording electrodes were implanted into the striatum and the hippocampus as part of a separate study. Bilateral guide cannulae were aimed at the mfb (AP:  $-3.6$ , ML:  $\pm 3.0$ , DV:  $-8.1$  mm; in one animal the coordinates were at AP:  $-1.8$ , ML:  $\pm 3.0$ , DV:  $-8.1$  mm, both at 7° towards the midline). Animals were given seven days to recover before behavioral training.

The two-compartment active avoidance procedures used in this study are identical to those used in a previous study (Jackson et al., 2008). Briefly, the animals were trained to avoid scrambled foot shocks (1 s, 0.1 mA) delivered in the dark compartment. Additional shocks (10 s apart) were administered until the animals made an escape, or after three shocks the animals were then manually placed in the light compartment. An inter-trial interval of 30 s was given before the next trial began. The performance criterion was eight successful avoidances in 10 consecutive trials. On the day after training, 10 trials with and 10 without PH DBS (100 Hz biphasic square waves, 0.1 ms duration at 0.1–0.3 mA) were administered in a counterbalanced fashion. The stimulation onset was  $\sim 1$  s prior to the avoidance trial (i.e. before the com-

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**Abbreviations:** DBS, deep brain stimulation; mfb, medial forebrain bundle; PD, Parkinson's disease; PFA, paraformaldehyde; PH, posterior hypothalamic nucleus; PPT, pedunculopontine tegmental nucleus; STN, subthalamic nucleus; 6-OHDA, 6-hydroxydopamine.

partment partition was removed) and was turned off after the animals stopped locomotion. The rate of successful avoidance and the avoidance latency were recorded. If there was no avoidance, the avoidance latency was recorded as 10 s. The following day, bilateral 6-OHDA lesions were made 30 min after desipramine administration (20 mg/kg in dH<sub>2</sub>O, i.p.) under halothane (1.5% minimum alveolar concentration) anesthesia. 6-OHDA (4  $\mu$ g/2  $\mu$ l, Sigma, St. Louis, MO, USA, in 0.9% saline with 0.5% ascorbic acid) was injected bilaterally using a pair of 10  $\mu$ l Hamilton gas-tight syringes at 0.5  $\mu$ l/min controlled by a syringe pump. The injection cannulae remained in place for 5 min after toxin delivery. This procedure was repeated four days later with 8  $\mu$ g/2  $\mu$ l to maximize the severity of akinesia. Three days after the second injection of 6-OHDA, avoidance behavior was re-tested.

Thirty micrometer cryotome slices were prepared from fixed (4% paraformaldehyde; PFA) and cryoprotected (20% sucrose) brains obtained immediately after the re-test session by transcardial perfusion (phosphate-buffered saline followed by 4% PFA). Implant tracts were visualized by Nissl staining. For a summary of the experimental protocol, see Fig. 1A. Statistical analysis was performed using SPSS 15.0 (SPSS, Chicago, IL, USA) and MATLAB (MathWorks, Natick, MA, USA). Analysis of variance (ANOVA) with repeated measures with Bonferroni correction ( $P < 0.008$ ) was used to test differences between mean avoidance latencies using the baseline condition as a reference. Fisher's exact test was used to compare the percentage of successful avoidances in each condition. Data are reported as mean  $\pm$  standard deviation with uncorrected  $P$ -values.

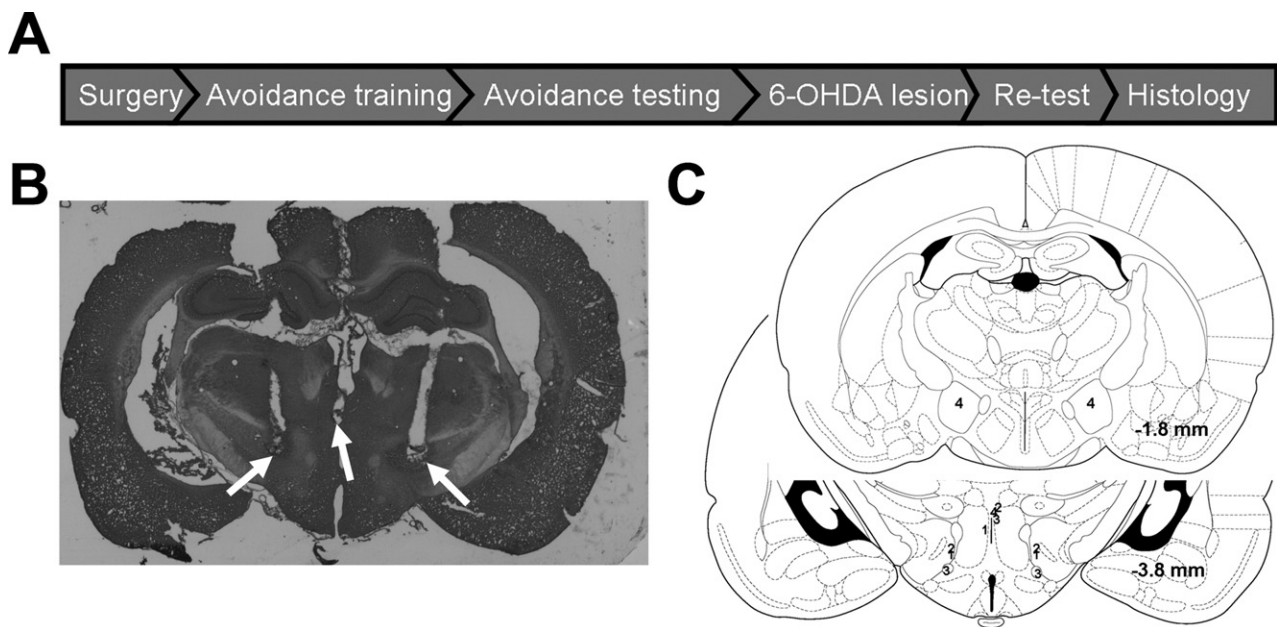
## RESULTS

A representative micrograph is presented in Fig. 1B. Eleven of the 15 animals survived the mfb 6-OHDA lesion but only four animals that had no aberrant unilateral behaviors before or after the lesion were used for analysis. The placements of stimulating electrodes and guide cannulae in all four animals are summarized in Fig. 1C. The placements corroborate well with previously reported be-

havioral observations where animals displayed increased locomotor activities with PH DBS (Bland and Vanderwolf, 1972; Jackson et al., 2008) and profound akinesia after mfb 6-OHDA lesion (Jolicoeur et al., 1991; Hayakawa et al., 1999). Fig. 2A clearly shows that the animals were able to avoid all foot shocks prior to 6-OHDA lesion (100% avoidance), and the application of PH DBS did not impact the rate of avoidance (100%; Fisher's exact test,  $P = 1$ ). After the lesion, there was a drastic decrease in avoidance rate (2.5% avoidance) in the absence of PH DBS (Fisher's exact test,  $P < 0.0001$ ). When PH DBS was applied, the animals were able to carry out avoidance 95% of the time, comparable to rates observed before the 6-OHDA lesion (Fisher's exact test,  $P = 0.12$ ). In terms of latency (Fig. 2B), the application of PH DBS did not alter the amount of time it took for intact animals to move across to the non-shock compartment ( $1.49 \pm 2.17$  s vs.  $1.40 \pm 1.78$  s;  $F_{(1,39)} = .039$ ,  $P = 0.845$ ). The 6-OHDA lesion virtually eliminated the avoidance behaviour ( $F_{(1,39)} = 458.54$ ,  $P < 0.0005$ ) and only a single avoidance was made by one animal at 1.87 s ( $9.80 \pm 1.29$  s). In lesioned animals, PH DBS offered improvement in avoidance latency ( $F_{(1,39)} = 151.25$ ,  $P < 0.0005$ ). However, these successful avoidances were made with a mean latency of  $5.01 \pm 2.17$  s, which is significantly slower than the pre-lesion baseline condition ( $F_{(1,39)} = 44.24$ ,  $P < 0.0005$ ).

## DISCUSSION

These data demonstrate the akinetic effects of bilateral 6-OHDA lesions in animals trained to perform an avoidance task. The application of PH DBS re-instated the avoidance behavior, although at a longer latency compared to non-lesioned performance. These findings are in



**Fig. 1.** The experimental protocol is summarized in (A). Histological sections were obtained and digitized to identify electrode (middle white arrow) and cannulae (flanking white arrows) tracts (B). The tips of electrodes and cannulae were reconstructed and summarized in (C) where each set of numbers corresponds to PH and mfb placements for each animal in the study.

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