Probing Dopaminergic Modulation via Subthalamic Stimulation: A Preclinical Perspective

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Abstract

Introduction: Subthalamic nucleus (STN) deep brain stimulation (DBS) is currently the gold standard symptomatic treatment for patients with levodopa therapy-induced complications in Parkinson's disease (PD). However, even though the efficiency of DBS is well recognized, to this date, it is not clear the influence of subthalamic stimulation on the dopaminergic system. Hence, the aim of this study is to investigate the effect of STN-DBS on striatal dopaminergic system in a rodent model of PD.

Method: This work was approved by the Ethics Committee on the Use of Animals at Hospital Sírio-Libanês (CEUA 2016/04). Male Wistar rats were subjected to the 6-hydroxydopamine (6- OHDA)-induced model of PD (left striatum, 12 ug) followed by the immediately ipsilateral implantation of STN electrode. Animals were divided into four groups: (i) Control (striatal saline + no electrode implantation), (ii) PD (striatal 6-OHDA + no electrode implantation), (iii) PD+-DBS OFF (striatal 6-OHDA + STN electrode implantation but not stimulated) and (iv) PD+DBS ON (striatal 6-OHDA + STN electrode implantation + active stimulation). PD+-DBS ON animals were stimulated 2h/day for 5 days (130 Hz, 60 μs, 0.1 mA). Motor evaluation was performed using cylinder test, immobility in the bar and open field test (OFT). Microdialysis samples were collected before the first and after the last session of DBS (7 and 12 days after the surgical procedure, respectively). After the last stimulation, animals were evaluated in apomorphine- induced rotation. Then, fresh and fixed tissue were for the evaluation of dopaminergic receptors (DR) expression, tyrosine hydroxylase immunoreactivity (TH-IR) and labelling of neuronal number. One and two-way ANOVA were used to statistically evaluate the results, where $p<0.05$.

Results: As expected, STN-DBS attenuated motor complications in the PD model, confirming its efficacy in our preclinical setup. Untreated PD animals showed increased striatal D1R and D2R expression ($p<0.01$ vs. control). Electrode implantation per se reduced this increase, while stimulated animals exhibited a significantly higher D1R/D2R ratio. PD and PD + DBS OFF groups showed a 30–50% reduction in striatal dopamine release between days 7 and 12 post- surgery ($p<0.01$ vs. baseline), whereas PD + DBS ON animals maintained baseline dopamine levels ($p>0.05$). Dopaminergic changes in non-treated PD animals were accompanied by reduced TH-IR in the substantia nigra (SN) and striatum ($p<0.001$ vs. control). In contrast, STN- DBS increased TH-IR in the SN and suppressed PD-induced contralateral rotations upon apomorphine administration, without interfering with the number of neurons in the SN.

Discussion:STN-DBS has the unique capability to reduce the equivalent dose of levodopa therapy, enabling the management of dyskinesia. Here we show that STN-DBS modulates dopaminergic circuitry by increasing the D1R/D2R ratio, promoting the switch from an anti- movement to a pro-movement setting while preventing the dopaminergic attenuation in the nigrostriatal pathway.

Conclusions: STN-DBS, rather than exerting a "neuroprotective" effect, facilitates a range of neuroplastic mechanisms promoting the modulation of dopaminergic surviving neurons. The enhanced activity of the direct motor pathway, driven by a more pronounced DR1 receptor response may partly explain the reduced levodopa dosage required to manage motor complications in PD.

References

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