

DBS for Parkinson's Disease: A Neurologist's Perspective

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Deep brain stimulation (DBS) is a welcome addition to armaments for treatment of Parkinson's disease (PD). Through a number of multicenter studies, it has been proven as a relatively safe and effective treatment for PD patients particularly when medical treatments are entangled by difficult motor complications. While it is not known how the DBS works in the human brain to improve symptoms of PD patients, it is somehow associated with actions of levodopa because the beneficial outcome of DBS is more predictable in PD patients with a good response to levodopa than those without.

Levodopa treatment remarkably improves motor deficits of PD patients. However, the long-term levodopa therapy frequently, but not always, induces motor fluctuations and/or dyskinesia. These response changes are a major disabling factor in patients with advanced PD. It is not surprising that marked motor fluctuations are the most common reason for PD patients to receive the DBS. As in the case of DBS, it is not clearly understood how levodopa improves parkinsonism and induces motor complications. Therefore, to understand how the DBS works, we explored how the DBS affects the actions of levodopa.

Central to motor fluctuations is a progressive shortening of levodopa response. Development of motor fluctuations follows a consistent pattern: initially, mild and long-lasting response ("stable response"), followed by greater response with shorter duration ("wearing-off"), and eventually, abrupt changes in response as if turned on and off by a switch ("on-off"). Motor fluctuations are best attributed to central mechanisms because plasma pharmacokinetics of levodopa do not differ between patients with stable response and those with fluctuating response. The time course of antiparkinsonian effects after a single dose of levodopa does not correspond to that of plasma levodopa concentrations (pharmaco-kinetic-dynamic dissociation), but does to that of striatal dopamine (DA) levels. The central pharmacokinetics of levodopa in the striatum includes transport from the plasma to the striatum, conversion to DA, vesicular storage of DA, release in the synaptic cleft, interaction with DA receptors, reuptake, and catabolism.

It has been inferred that motor fluctuations result from the loss of buffering capacity of DA terminals, rendering striatal extracellular DA levels fluctuating according to plasma levodopa levels. Recent PET studies of raclopride displacement have provided direct evidence for this view. PD patients who had shown significant levodopa-induced DA efflux in the putamen developed motor fluctuations later on whereas those who had not shown such DA efflux did not develop motor fluctuations. Similar fluctuations of DA levels were observed in the putamen of PD patients with levodopa-induced dyskinesias, and in the ventral striatum of PD patients with DA dysregulation syndrome. Experimental studies in a rat model of PD also showed a robust levodopa-induced DA efflux in the striatum of

dyskinetic rats. These findings demonstrate that levodopa-induced DA efflux in the striatum plays a pivotal role in the development of levodopa-induced complications in PD patients.

The most significant change at the conversion of stable response to fluctuating response is the shortening of the decay time. It is a common belief that the shortening of decay time is caused by progressive loss of DA terminals in the striatum of PD patients (hence, the storage capacity of DA). Recent evidence however suggests the contrary. We investigated the role of DA terminal loss in the development of motor fluctuations using PET with [^{11}C]DTBZ, as an in vivo marker for DA terminals, in PD patients with asymmetric parkinsonism. Levodopa response after a single dose of the drug, which was characterized by the finger-tapping test, showed significantly shorter duration and decay time on the worse side (i.e. more symptomatic side). However, the asymmetry of DTBZ BP in the putamen did not correlate significantly with that of the decay time, suggesting that shortening of the decay time was not proportional to the DA terminal density in the striatum. Moreover, animal experiments in a rat model of levodopa-induced dyskinesia provided evidence that pulsatile treatment with levodopa had enhanced levodopa-induced DA efflux in the DA-denervated striatum. These observations indicate that fluctuations of DA levels in the striatum can be induced by levodopa treatment in PD patients.

While shortening of the decay time is the most characteristic findings, motor fluctuations accompany other changes in the levodopa response: for instance, sigmoidal changes of the concentration-response curve, and/or a gradual loss of long duration response. These changes, which cannot be explained by the loss of DA terminals, strongly suggest that postsynaptic factors are also important in the pathogenesis of motor fluctuations. Putting together, converging evidence supports the view that fluctuations of DA levels in the striatum play a crucial role in the development of motor fluctuations, and can be enhanced by functional changes and/or by loss of DA terminals in the striatum.

STN DBS places the electrode in the postsynaptic nuclei of the basal ganglia circuitry that generates constant neural stimulations; thus, it could counteract the effects of fluctuating DA levels in the striatum on postsynaptic neurons evoked by pulsatile levodopa treatment. We investigated the effects of STN DBS on the long duration response (LDR) and the short duration response (SDR) to levodopa in 48 patients with PD who underwent bilateral STN-DBS. Levodopa tests were performed before and 6 months after DBS surgery. Off-UPDRS scores (i.e. changes in LDR) induced by STN-DBS over 6 months showed a significant correlation with pre-DBS baseline off-UPDRS scores ($r=0.611$, $p<0.0001$). Multiple regression analysis revealed highly significant correlations between the magnitude of SDR prior to DBS and all three components of $\Delta\text{UPDRS III}$ scores after 6 months' STN-DBS (magnitude of SDR before DBS = $0.602*a + 0.981*b + 0.803*c + 4.924$; $r=0.795$, $p<0.0001$; a: ?LDR, b: immediate effect of DBS, c: magnitude of SDR). Comparisons of the SDRs over one year after the STN DBS, which were assessed by the finger tapping test, also showed progressive improvement of tapping rates at the off state (i.e. off levodopa), in keeping with earlier observations in LDR. Taken together, these observations suggest that STN-DBS improves motor fluctuations by (1) improving LDR, the effect of which persists even after DBS is turned off, and (2) improving parkinsonism at the off state (off levodopa), the effect of which appears only when the DBS is turned on.

In conclusion, our data suggest that STN DBS improves motor fluctuations by a dual mode of action: the delayed effect on the long duration response to levodopa, and the immediate effect of turning the stimulator on. These observations have implications as to the timing of the STN DBS surgery.