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Check the 'Active Ingredients' of Your Medications

Comment on 'Does Dopamine Still Have a Leading Role in Advanced Parkinson's Disease after Subthalamic Stimulation?' (Stereotact Funct Neurosurg 2008;86:184–186)

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In this paper, the authors give a rationale for an extrastriatal dopaminergic pathway in Parkinson's disease (PD) based on a clinical observation. They describe a young patient who underwent successful placement of bilateral subthalamic nucleus (STN) deep brain stimulation electrodes (DBS). He had an excellent clinical response at first to stimulation, with improvement in UPDRS and dyskinesia scores while not taking any levodopa, although he did take the dopamine agonist cabergoline.

About 14 months after surgery the patient had an acute motor worsening. The only apparent reason for this was his taking an antihistamine to counter a contact allergy. One of the components of this drug was fluphenazine, a potent dopamine antagonist. Several days after stopping this medication the patient regained his previously functional postoperative status.

The authors suggest that since the STN is 'downstream' from the striatal feedback loops of the basal ganglia circuits as they are currently understood, a dopamine antagonist would not inhibit the benefits of STN DBS by an effect on the striatum. Rather, inhibition of extrastriatal dopaminergic pathways may have been to blame for this patient's decline after taking fluphenazine. The possibility remains that there was an inhibitory effect by fluphenazine on striatal dopaminergic circuits that were enhanced with cabergoline.

This is an interesting report that the authors reasonably propose as a spur to study alternate physiological pathways for PD. From a purely practical point of view, clinicians should be alert to the fact that commonly available antiallergic medications may contain dopamine antagonists that can worsen their patients' parkinsonian symptoms.

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DBS and Dopamine

Comment on 'Does Dopamine Still Have a Leading Role in Advanced Parkinson's Disease after Subthalamic Stimulation?' (Stereotact Funct Neurosurg 2008;86:184–186)

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How does DBS improve symptoms in PD? To a first approximation, the current concept is the following: As a downstream consequence of striatal dopamine denervation, basal ganglia output (GPI and its glutamatergic upstream partner, STN) have excessive and abnormally patterned activity. DBS of STN or GPI 'corrects' this abnormal activity, allowing thalamocortical pathways and/or brainstem structures receiving BG outflow to function more normally. As PD progresses, symptoms arise that are resistant to DBS (such as hypophonia, postural instability, and dementia) but these are also resistant to dopaminergic pharmacotherapy, and are thought to be due to involvement of non-dopaminergic pathways that also degenerate in PD.

If this view is entirely correct, one might not expect further compromise of basal ganglia dopaminergic pathways to affect the ability of STN-DBS to suppress L-dopa-responsive cardinal PD symptoms. Hence the interest of this case report by Jabre et al. They report that a patient who had considerable benefit from STN DBS loses that benefit for 3 days following inadvertent ingestion of the D1, D2 antagonist fluphenazine. This finding is used to argue that STN DBS must act in part via a dopaminergic mechanism: either striatal dopamine, or the less dense but potentially important dopaminergic innervation of other BG nuclei, including a dopaminergic innervation of the STN itself.

Prior neurochemical studies of the effects of DBS on DA release in the basal ganglia are not entirely consistent. In humans, it has been shown that STN DBS does not alter striatal dopamine release [1]. However, in rat brain slices, STN DBS does result in depolarization of nigral dopaminergic cells (which could result in striatal DA release in intact animals) [2]. In intact parkinsonian rats chronically treated with L-dopa, STN DBS alters the responsiveness of striatal cells to L-dopa [3]. The current literature leaves open the possibility that STN DBS may act in part by a mechanism dependent on dopaminergic transmission, including extrastriatal dopaminergic transmission, but does not confirm this view resoundingly.

Perhaps a more direct explanation for the finding in this case report is that STN DBS does not alter all the striatal DA-mediated abnormalities in PD, but produces only a partial correction which in most patients is sufficient to suppress the cardinal parkinsonian symptoms that are mediated by dopamine loss. Thus, STN DBS patients could still rely on some residual function of nigrostriatal DA circuits, even if STN DBS itself does not affect striatal dopamine release in humans. This scenario is consistent with the observation that most PD patients receiving STN DBS experience optimal motor function with a combination of DBS and dopaminergic pharmacotherapy. A further blockade of striatal DA transmission could then worsen parkinsonian symptoms beyond the ability of STN DBS to compensate, as illustrated in this case report.

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The Paradoxical Role of Dopamine after Subthalamic Nucleus Deep Brain Stimulation – Downstream Is Upstream in a Circuit Diagram

Comment on 'Does Dopamine Still Have a Leading Role in Advanced Parkinson's Disease after Subthalamic Stimulation?' (Stereotact Funct Neurosurg 2008;86: 184–186)

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Is anyone else as troubled as I am by the fact that patients must have a good response to levodopa to have a good response to subthalamic nucleus (STN) stimulation? It does not bother me that – in patients that have a good response to levodopa – the ef-

fects of STN stimulation and levodopa are similar in magnitude: they both ostensibly rectify the circuit dysfunction at the globus pallidus internus (GPi) level and beyond caused by the dopaminergic (DA) deficit. What bothers me is that patients who *do not* have a good levodopa response *do not* respond well to STN stimulation. I thought that poor levodopa response was due to insufficient numbers of DA terminals in the putamen to take up and metabolize levodopa to DA but that STN stimulation works 'downstream' of the putamen. Indeed, this observation came as a surprise to many movement disorder specialists as well, as evidenced by the overall lower levodopa responsiveness (and STN benefits) in some centers that adopted STN stimulation the earliest [see 1]. They apparently did not predict, based on the prevalent DeLong model of basal ganglia circuitry, that response to STN stimulation (whether you believe it is inhibitory or excitatory) would require that patients respond to levodopa. So why is this the case? The potential explanations cut right to the central question that to this day remains incompletely understood: what is the mechanism of action of STN stimulation? Although in this issue Jabre et al. [2] present only a single case, their finding is quite provocative and may shed light on the question of how STN deep brain stimulation (DBS) works and the role of levodopa in its effectiveness.

Jabre et al. [2] describe the acute deterioration in parkinsonian symptoms of a patient with ongoing confirmed functioning STN stimulation triggered by a single dose of fluphenazine, a potent D1/D2 antagonist (in addition to its effects on other neurotransmitter systems). The patient had a 75% response to levodopa challenge before surgery, and similarly STN stimulation led to a 73% reduction in the Unified Parkinson's Disease Rating Scale motor subscale score. All parkinsonian medication was initially withdrawn but non-motor findings of apathy prompted the institution of cabergoline, a mixed D1/D2 agonist, i.e. this was not ostensibly to treat motor symptoms. After the inadvertent fluphenazine dose, the patient's motor score response deteriorated – on STN stimulation and on cabergoline – to 58%, including increased akinesia, rigidity, tremor and axial symptoms. The patient's preoperative levodopa-induced dyskinesia was 83% alleviated by STN stimulation and withdrawal of levodopa treatment. However, the patient experienced mild STN stimulation – evoked facial and right upper extremity dyskinesia, and after fluphenazine this temporarily disappeared. Thus, as the authors point out, it appeared that fluphenazine blocked the effects of STN stimulation and/or blocked the effects of ongoing DA activity. These possibilities are intriguing or seemingly mundane, respectively, but both are actually instructive with regard to mechanisms of STN stimulation.

Is there ongoing DA activity that contributes to clinical performance during 'downstream' STN stimulation? This would seem at first glance not to be the case when one considers that STN stimulation leads to clinical improvements in the 'off' medication state (off medication/on stimulation) that are similar in magnitude to the response to medication (on medication/off stimulation) and that adding levodopa to STN stimulation leads to essentially no greater response (on medication/on stimulation) [see 1]. The lack of additivity of levodopa and STN stimulation implies that they operate by the same mechanism (e.g. rectification of circuit activity at and beyond GPi). However, is the off medication/on stimulation state the same as the fluphenazine/on stimulation state? No! In the 'off' medication state, it is perhaps overlooked