INVITED EDITORIAL

This Invited Editorial accompanies a Research Paper, see page 441

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2022, Volume 56, no. 5, pages: 385–388
DOI: 10.5603/PJNNS.a2022.0061

ISSN: 0028-3843, e-ISSN: 1897-4260

Does deep brain stimulation stimulate metabolism?

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Over the past two decades, there has been a substantial increase in the appreciation and study of non-motor features of Parkinson's Disease (PD) [1]. Orthostatic hypotension, constipation, and REM sleep behaviour disorder are examples that can have a significant impact on patient quality of life. Weight loss is common in PD, but has not received as much attention as other non-motor signs, perhaps because the negative consequences are delayed and less direct than those of other non-motor signs. There are likely to be multiple factors contributing to PD-associated weight loss, such as increased energy expenditure due to motor symptoms, disrupted hypothalamic metabolic regulation, and reduced dietary intake [2]. Despite our limited understanding of these mechanisms, it is important to consider this disease milieu before drawing conclusions about the metabolic effects of PD treatments.

Deep brain stimulation (DBS) is used to treat a variety of conditions through modulation of brain networks [3, 4]. DBS targeting the globus pallidus interna (GPi) or subthalamic nucleus (STN) improves PD-related motor symptoms and prolongs "ON" time [5, 6]. The GPi and the STN are roughly equivalent with respect to efficacy [7, 8]. Choosing between these targets is based on institutional preference and/or, more importantly, patient characteristics. Elsewhere in this issue, Samborska-Ćwik et al. have reported weight gain and several negative metabolic consequences in PD patients who underwent STN DBS [9]. These may represent direct stimulation-related effects and/or indirect consequences of DBS clinical effects, e.g. improved motor symptoms.

There have been numerous reports of weight gain following STN-DBS [10–14], although the mechanisms remain elusive. Head-to-head comparisons showing a greater likelihood of post-surgical weight gain following STN targeting versus GPi suggest that the STN may have more direct connections to metabolic centres [14, 15], but differential effects on motor symptoms and subsequent medication management could explain why the STN appears to be more obesogenic. Sauleau et al. found that STN targeting was associated with greater weight gain, a reduction in UPDRS III total "ON" scores, UDPRS IV total scores, UPDRS IV dyskinesia score, UPDRS IV fluctuations score, and levodopa equivalent daily dose (LEDD) [14].

One might hypothesise that decreased metabolic demand from improved motor symptoms could cause weight gain. Previous metabolic studies have shown that resting energy expenditure is increased in PD by 20–51% in ON and OFF-medication states [2]. Rigidity and dyskinesias are especially metabolically demanding, and two studies have shown that increased resting energy expenditure was negated when severe dyskinesias were excluded [16–18]. A more significant reduction of LEDD may reflect a medication effect on weight gain, and could be expected in patients with post-DBS lowering of their dopamine agonists, which has been reported to increase insulin sensitivity [19]. Levodopa has been reported to induce hyperglycaemia and hyperinsulinaemia, and so dose reduction seems unlikely to be obesogenic [19, 20].

Dopamine is a probable factor in weight gain and metabolism due to its effects on pancreatic function (Fig. 1). Dopamine is produced locally in the pancreas, and at low levels activates D2/3 receptors of α and β pancreatic cells to inhibit release of glucagon and insulin, respectively [21]. At higher levels, dopamine may bind to adrenergic receptors of α and β pancreatic cells, resulting in enhanced inhibition of insulin secretion but stimulation of glucagon secretion [21]. This may in part explain reports of hyperglycaemia following levodopa administration [20]. Reports of levodopa-associated hyperinsulinaemia may be related to indirect effects of dopamine on the pancreas by way of D2 receptor-mediated downstream reduction in norepinephrine and epinephrine release from sympathetic nerve endings and the adrenal medulla, respectively [22].

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Received: 24.08.2022 Accepted: 25.08.2022 Early publication date: 15.09.2022

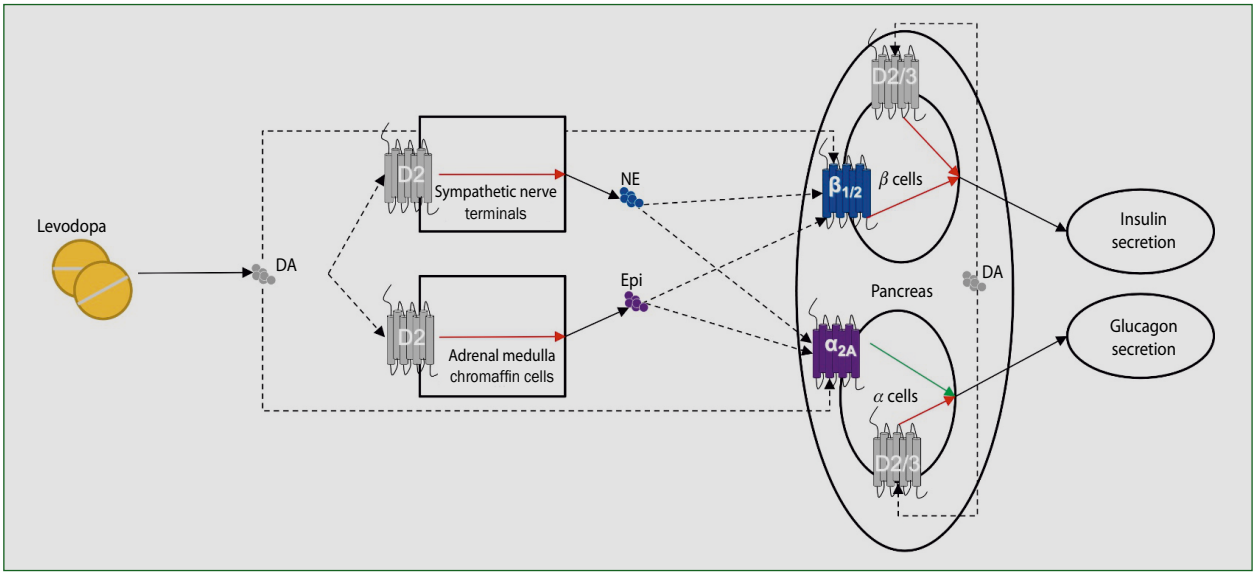

Figure 1. Dual effects of dopamine on metabolic regulation. Within pancreas, locally released dopamine (DA) activates high affinity D2/3 receptors (*grey*), thus inhibiting release of insulin and glucagon. Off-target activation of lower affinity adrenergic receptors (*blue* and *purple*) with higher dopamine concentrations, e.g. levodopa dosing, may further inhibit insulin release but stimulate glucagon release. Norepinephrine (NE) and epinephrine (Epi) released by presynaptic sympathetic nerve terminals and chromaffin cells of adrenal medulla stimulate α cell glucagon secretion and inhibit β cell insulin secretion. Activation of D2 receptors on sympathetic nerve terminals and chromaffin cells inhibits NE and Epi release, leading to more insulin release and less glucagon release. Red arrows indicate inhibition. Green arrow indicates excitation/enhancement

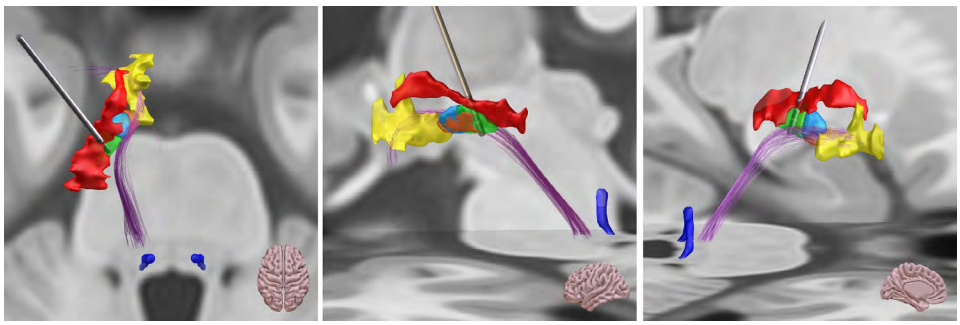

Figure 2. 3D MRI reconstruction of deep brain stimulation (DBS) lead targeting subthalamic nucleus (STN). Axial (*left panel*), lateral sagittal (*centre panel*), and medial sagittal (*right panel*) images show well-positioned lead in sensorimotor region of STN and its neighbouring structures. Zona incerta (*red*), lateral hypothalamus (*yellow*), STN sensorimotor (*green*), STN associative (*light blue*), STN limbic (*orange*), locus coeruleus (*dark blue*), and medial forebrain bundle (*purple*)

Candidate sites for direct stimulation-induced metabolic effects include the lateral hypothalamus (LH), fibre tracts of metabolic centres, and/or non-motor regions of the STN. There are conflicting reports as to which STN lead locations are the more obesogenic. One study found that more medial active contacts were associated with greater weight gain ($r = -0.55$) [13], but a separate study found precisely the opposite effect ($r = 0.51$) [11]. Both papers cited proximity to the hypothalamus as a potential explanation. Weight gain due to off-target current spread into the LH is implausible because well-positioned STN leads target the ventrolateral portion of the nucleus, which is several millimetres from hypothalamic structures (Fig. 2). Even if current spread reached the LH, this should actually cause weight loss, based on animal studies of high frequency (180–200 Hz) stimulation to this region [23]. Moreover, the LH has been targeted to treat obesity, given its centrality to circuits involved in hunger/satiety [24, 25]. Typical stimulation parameters of the STN are lower than those used to stimulate the LH, and the net inhibitory/excitatory effect of these lower frequencies at the LH is unknown. The case for decreased satiety does not seem to be particularly strong because weight gain has been reported with both STN and GPi-targeted patients despite no change in food intake, and rodent food intake was not significantly changed with

LH stimulation-induced weight loss [14, 23]. However, more medialised leads may stimulate associative or limbic regions of the STN which could lead to impulse control disorders e.g. binge eating. The study associating medial active contacts with greater weight gain found a positive correlation between food intake and weight gain 18 months after surgery [13].

The locus coeruleus (LC) is the principal source of cerebral noradrenergic projections and degenerates in PD [26]. STN neurons have both α_1 and α_2 receptors, and there is a complex interaction between dopaminergic nigrostriatal projections and regulation of the noradrenergic system in PD. Guimarães et al. have proposed noradrenergic dysfunction as an explanation of weight loss in PD [27]. In their model, noradrenergic dysfunction within a network including the LC, striatum, subthalamic nucleus, ventromedial hypothalamus, and lateral hypothalamus causes decreased noradrenaline levels in the central nervous system but increases peripheral noradrenaline. The subsequent increase in basal sympathetic nervous system activity results in weight loss. They have also proposed that STN-DBS may activate efferent or afferent fibre bundles crossing the STN, thus stabilising noradrenergic modulation leading to weight gain. DBS targeting the ventral striatum (nucleus accumbens) and ventral capsule has been used to treat patients with obsessive-compulsive disorder and addiction [28]. Weight loss and gain have been reported with this targeting, but a recent study found weight increases to be associated with medial/apical stimulation and connectivity to hypothalamic areas and the bed nucleus [28]. Given the connectivity between striatonigral projections, including the nucleus accumbens, and the lateral hypothalamus via the medial forebrain bundle (MFB) and the proximity of this fibre tract to the STN, it seems plausible that current spread to MFB fibres could affect weight and alter metabolic functions (Fig. 2).

The recent work by Samborska-Ćwik et al. [9] has begun to untangle the complex cascade of glycaemic control in PD and how it is altered with DBS. While most work in this field has focused on weight changes and glucose effects, these authors have begun to uncover changes in the metabolism of other macromolecules, e.g. lipids. Given that lipid metabolism is influenced by insulin-mediated glycaemic control, it seems likely that these changes represent a concert of downstream changes from a central effect within the brain. While various mechanisms have been proposed, many studies have implicated DBS through off-target effects on structures outside of the STN, with those having more sensorimotor STN locations showing less weight gain.

Many factors should be considered when choosing the appropriate DBS target for a patient with PD. These factors primarily include the motor symptoms, but perhaps a person's pre-surgical metabolic state should also be factored into target selection. One size does not fit all.

Conflicts of interest: *None.*

Funding: *None.*

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