

The role of dopamine in the modulation of gastrointestinal motility in a rat model of Parkinson's disease

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Parkinson's disease (PD) is a multi-system, complex disorder characterized by the involvement of selected neuronal populations throughout the central and peripheral nervous systems. Although PD is considered a prototypical movement disorder, PD patients also experience numerous non-motor symptoms; dysfunctions affecting the gastrointestinal (GI) tract are extremely frequent in these patients, with severe constipation being the most prominent manifestation.

GI motility is controlled by various mechanisms, acting at both central and local levels. Local control is exerted by the enteric nervous system (ENS), where the role of dopaminergic neurotransmission is being increasingly recognized. Dopamine, tyrosine hydroxylase (TH), and the dopamine transporter co-localize within a subset of ENS neurons; in the ENS, dopamine has an inhibitory effect mediated by the activation of pre-junctional D₂ receptors located on cholinergic, excitatory neurons of the myenteric plexus.

A crucial node in this network might be the dorsal motor nucleus of the vagus (DMV), a cholinergic nucleus located in the medullary region of the brainstem, which provides extensive parasympathetic innervations to the ENS plexuses. The DMV is affected by PD pathobiology since the very early stages of the disease; moreover, DMV neuronal activity is susceptible to dopamine-mediated modulation.

In our study, we sought to investigate all these aspects using a classic rodent model of PD. Sprague-Dawley rats underwent a unilateral lesion of the nigrostriatal tract by stereotaxical injections of 6-hydroxydopamine (6-OHDA) into the right medial forebrain bundle. The following evaluations were conducted in 6-OHDA lesioned and sham-operated animals: 1) analysis of peristaltic activity in isolated segments of distal colon; 2) analysis of enteric dopamine levels and expression of D₂ receptors; 3) immunohistochemical investigation of neuronal activity (Delta-FosB expression) in the DMV.

The analysis of peristaltic activity did not show differences in the parameters considered (e.g. peak pressure, accommodation, frequency) between the two groups, in basal recording. However, when colonic segments were exposed to dopamine agonist rotigotine (0.3-3 μM), we observed that the drug completely abolished peristalsis in control animals – as expected - but not in the lesioned rats. A trend toward a reduced expression of D₂ receptors was observed in the colon of 6-OHDA lesioned rats, which was associated with moderate, nonsignificant increases in tissue levels of dopamine. Animals bearing the 6-OHDA induced lesion showed increased Delta-FosB expression, compared to control animals, in DMV neurons.

We have previously demonstrated that rats with massive, unilateral nigrostriatal lesion induced by 6-OHDA develop marked constipation combined with reduced nNOS expression in the myenteric plexus of specific intestinal regions. The present study suggests that the loss of SN dopaminergic neurons may trigger reciprocal neurochemical alterations in the ENS, with an increased dopaminergic tone that may account for the altered functional response to DAergic stimulation. These changes seem to be associated with (or sustained by) an increased neuronal activity in the DMV, which represents the crucial crossroad in the alteration of the brain-gut crosstalk taking place in PD.