Gastrointestinal symptoms and local oxidative stress in a model of Parkinson's Disease in rats

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Background: Parkinson's disease (PD) is the second most common neurodegenerative pathology, after Alzheimer's disease, and its primary cause is not clear yet. Various converging mechanisms are likely to be involved in PD pathogenesis, including genetic and environmental factors, proteolytic defects and neuroinflammation; oxidative stress may be the final effector of these mechanisms, as signs of oxidative damage have been reported both centrally (1) and peripherally (2) in PD patients. Besides the classical motor symptoms, more than 50%(3) of PD patients experience gastrointestinal (GI) dysfunctions, including constipation and gastroparesis. Despite the high incidence and impact on patient's quality of life, the mechanisms underlying gastrointestinal symptoms have not been completely elucidated and local levels of oxidative stress have not been measured.

Aim: The aims of this study were to 1) characterize GI symptoms using a conventional animal model of PD 2) follow their progression over time 3) quantify oxidative stress in GI tissues, viewed as a possible mechanism causing peripheral neurodegeneration.

Methods: All the experiments were performed in accordance with Guiding Principles in the Care and Use of Animals (DL 116/92). To obtain a PD-like selective central dopaminergic lesion, rats were unilaterally injected with 6-OH-Dopamine (6-OHDA) in the medial forebrain bundle (*LESIONED*) and controls (*SHAM*) received the vehicle by the same stereotaxic injection. Fecal output (g/5hrs) was monitored for 8 weeks and GI transit was monitored *in vivo* at different time points by radiological analysis. Analysis of radiographic contrast studies was made according to the scoring proposed by Cabezos et al.(4) by observers unaware of the treatment. At the end point (8 weeks from central lesion) GI transit was measured analyzing the absorbance of GI segments collected after 1 hr from an unabsorbable dye gavage and expressed as geometric center. Tissues from different GI regions were collected for malondialdehyde (MDA) spectrophotometric measurement (nmol/g of tissue), index of lipoperoxidation.

Results: Central lesion caused an overall impairment of GI transit, as shown by a lower fecal output (4.52±0.35 g/5hrs *SHAM* vs 3.13±0.50 g/5hrs *LESIONED* at week 4, $p<0.05$; 4.51±0.25 g/5hrs *SHAM* vs 2.89±0.55 g/5hrs *LESIONED* at week 6; $p<0.05$; 3.98±0.41 g/5hrs *SHAM* vs 3.33±0.57 g/5hrs *LESIONED* at week 8). Radiological analysis also revealed a delay in gastric emptying, constipation, and progression of GI dysmotility with time. These findings were consistent with geometric center data (7.88±0.24 *SHAM* vs 6.11±0.71 *LESIONED*, $p<0.05$), estimated after 8 weeks. Interestingly, MDA levels were significantly ($p<0.05$) increased in stomach (23.65±1.62 nmol/g of tissue *SHAM* vs 95.27±24.72 nmol/g of tissue *LESIONED*), ileum (16.13 ±1.48 nmol/g of tissue *SHAM* vs 45.67±10.60 nmol/g of tissue *LESIONED*) and colon (122.77±40.92 nmol/g of tissue *SHAM* vs 525.32±120.60 nmol/g of tissue *LESIONED*), regions affected by PD-induced dysmotility.

Conclusions: Our data show that a PD-like central lesion leads to the development of GI dysmotility in rats. GI dysfunction evolves with time, resulting in slow GI transit, due to delayed gastric emptying and constipation. GI MDA levels are increased in those areas affected by altered motility. Our data are consistent with findings obtained in plasma of PD patients(2) and suggest that local oxidative stress might account for intestinal changes causing transit dysfunction. The possible protective effect of antioxidant supplementation still remains to be investigated.

References:

(1) **Jenner P** et al. Ann Neurol. 1992; 32 Suppl: S82-7.
(2) **Sanyal J** et al. Eur Rev Med Pharmacol Sci. 2009; 13(2): 129-32.
(3) **Winge K** et al. J Neurol Neurosurg Psychiatry. 2003; 74(1): 13-19.
(4) **Cabezos P.A.** et al. Autonomic Neuroscience: Basic and Clinical 2008; 141: 54–65.