

EFFECTS OF L-DOPA/BENSERAZIDE CO-TREATMENT ON COLONIC EXCITATORY CHOLINERGIC MOTILITY AND ENTERIC INFLAMMATION FOLLOWING DOPAMINERGIC NIGROSTRIATAL NEURODEGENERATION

1)Pellegrini C. 2)Antonoli L. 3)Colucci R. 4)Tirota E. 5)Gentile D. 6)Benvenuti L. 7)Segnani C. 8)Ippolito C. 9)Levantis G. 10)Cerri S. 11)Blandini F. 12)Barocelli E. 13)Ballabeni V. 14)Bernardini N. 15)Blandizzi C. 16)Fornai M.

University of Pisa

Introduction. Gastrointestinal disturbances in Parkinson's disease (PD) are prominent non-motor features of the disease (1), represented mainly by digestive motor abnormalities associated with bowel inflammation (2). The mainstay treatment of PD is represented by levodopa (L-DOPA) plus DOPA-decarboxylase inhibitors (3). However, the possible influence of these drugs on colonic inflammation and dysmotility in PD are unknown. This study examined the effects of L-DOPA plus benserazide (L-DOPA/BE) on alterations of colonic motility and inflammatory markers in rats with 6-hydroxydopamine (6-OHDA)-induced nigrostriatal dopaminergic denervation.

Methods. Neurodegeneration was induced by intra-nigral 6-OHDA injection. In particular, rats received 6-OHDA (dissolved in saline solution containing 0.02% of ascorbic acid) or its vehicle (controls) unilaterally into two sites of the right medial forebrain bundle relative to bregma (9 $\mu\text{g}/3 \mu\text{L}$) and dural surface (7.5 $\mu\text{g}/3 \mu\text{L}$) (4). 6-OHDA animals were treated orally with L-DOPA/BE (6/15 mg/Kg/day) for 28 days, starting 28 days after toxin injection. At the end of treatment, in vivo colonic transit was evaluated by a radiologic assay. Electrically stimulated (ES) cholinergic contractions were recorded in vitro from colonic preparations, while acetylcholine release was measured in the incubation media. Choline acetyltransferase (ChAT) and glial fibrillary acidic protein (GFAP) expression as well as eosinophil and mast cell density were examined in the colonic wall by immunohistochemistry. Colonic TNF and IL-1 β levels were also assayed.

Results. 6-OHDA animals displayed: 1) decrease in in vivo colonic transit; 2) impairment of ES-induced cholinergic contractions; 3) decreased acetylcholine release from myenteric nerves; 4) decrease in ChAT and increase in GFAP myenteric immunopositivity; 5) increase in eosinophil and mast cell density; 6) increase in TNF and IL-1 β levels. Treatment with L-DOPA/BE caused an improvement of in vivo and in vitro colonic motor activity, a normalization of acetylcholine release and ChAT immunopositivity, as well as pro-inflammatory cytokine patterns, ganglionic GFAP levels, eosinophil and mast cell density.

Conclusion. The replenishment of dopamine levels in the central nervous system by treatment with L-DOPA/BE ameliorated colonic dysmotility, arising from dopaminergic nigrostriatal denervation, through a normalization of myenteric cholinergic neurotransmission, along with an improvement of colonic inflammation.

References

1. Pellegrini C et al. (2016) Neurogastroenterol Motil. 28,1781-1791

2. Pellegrini C et al. (2016) *J Neuroinflammation* 13:146
3. Brooks DJ (2008) *Neuropsychiatr Dis Treat.* 4, 39-47.
4. Blandini F et al. (2009) *Neurosci Lett* 467, 203-207.