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Gastrointestinal Dysmotility in the P+L Rat Model of Parkinson's Disease

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Introduction: Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder primarily caused by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). PD is characterized by motor manifestations such as bradykinesia, resting tremor, and rigidity, which is frequently preceded by gastrointestinal (GI) dysfunction, particularly constipation for decades. [1] Braak, et. Al. hypothesized that PD pathology originates in the GI tract and then travels retrograde via the vagus to the brain. [2] We showed the Braak hypothesis can be modeled in the rat by administration of subthreshold doses of Paraquat (P) and Lectin (L) to cause aggregation of misfolded α-synuclein in the GI tract that ascends retrograde via the vagal nerves into the medulla and then via the nigro-vagal pathway to initiate PD-related pathology in the SNpc. [2-4]

Objectives: This study aimed to investigate the effects on total oro-anal transit time (TOTT) in the P+L rat model of PD and to explore the temporal course of the onset of GI dysfunction and motor symptoms in this model.

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Methods: Carmine, red dye solution (75 mg/mL in 0.9% carboxymethyl cellulose) was administered via oral gavage to rats (n=16). [5] TOTT was recorded as the interval in minutes between gavage and the first appearance of carmine, red in the feces over 24 hours with video recording at baseline, 1-, 2- and 4 weeks post P+L exposure. [5] All rats were exposed to oral P+L for 7 days as we have previously described causing parkinsonism as evidenced in a rodent behavioral battery of tests [4].

Results: All rats exhibited a significant increase in TOTT at 1- (p-value 0.142,12.4%), 2- (p=0.27, 9.4%), and 4 weeks (p=0.003, 24.3%) post-exposure compared to baseline. Parkinsonism as expected began at 2 weeks and was robustly established at 4 weeks in all rats that were levodopa responsive. Histological analysis revealed nigrostriatal neurodegeneration and pathologically misfolded alpha-synuclein in the SNpc neurons.

Conclusions: TOTT is delayed in the P+L rat model of PD and GI dysmotility appears to precede the onset of motor manifestations mimicking human disease. Therefore, the P+L rat model may be suitable for experimental therapeutics that target the GI tract to mitigate PD pathology in the gut and the brain.

Keywords: Parkinson's Disease (PD), Gastrointestinal Dysfunction, GI Symptoms, Paraquat, Nigro-Vagal Impairment, Alpha-Synuclein, Gut and Brain, GI Dysmotility

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