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A progressive rat model of Parkinson's disease featuring prodromal indications, early asymmetry, progressive development, anatomical spread of synuclein aggregates, and late-stage cognitive deficits.

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The development of effective neuroprotective therapies for Parkinson's disease (PD) has been severely hindered by the lack of an appropriate animal model for preclinical screening. Indeed, most models currently available are either acute in nature or fail to recapitulate all characteristic features of the disease. Here, we present a novel progressive model of PD, with behavioural and cellular features that closely approximate those observed in patients.

Chronic exposure to dietary phytosterol glucosides has been found to be neurotoxic. When fed to rats, *β*-sitosterol *β*-d-glucoside (BSSG) triggers the **progressive** development of parkinsonism, with clinical signs and histopathology beginning to appear *following cessation* of exposure to the neurotoxic insult and continuing to develop for several months. Here, we further characterize the progressive nature of this model, its non-motor features, the anatomical spread of synucleinopathy, and response to levodopa administration.

Adult male Sprague Dawley rats received daily feedings of either plain flour pellets or flour pellets containing BSSG (3 mg) for 4 months. At 4 months, toxin feeding was terminated. Animals were monitored for locomotor activity, coordination, olfaction, and cognitive function beginning immediately following cessation of toxin exposure and continuing throughout the duration of the study. Animals were sacrificed at 4, 6, 8, and 10 months following initial toxin exposure. Tissues were assayed for the loss of dopaminergic neurons, appearance of inflammatory cytokines, proteasome activity and abnormal protein aggregates.

Chronic exposure to BSSG resulted in the progressive loss of nigrostriatal dopaminergic neurons. At approximately 4 months following initiation of BSSG exposure, animals displayed the early emergence of an olfactory deficit in the absence of significant dopaminergic nigral cell loss or locomotor deficits. Locomotor deficits developed gradually over time, initially appearing as locomotor asymmetry and developing into akinesia/bradykinesia; this was reversed by levodopa treatment. Late-stage cognitive impairment was observed in the form of spatial working memory deficits, as assessed by the radial arm maze. In addition to the progressive loss of TH^+ cells in the substantia nigra, the appearance of insoluble intracellular α-synuclein aggregates was also observed to develop progressively and spread from olfactory bulb to substantia nigra and, finally, hippocampal and cortical regions (1). The slowly progressive nature of this model, together with its *construct*, *face* and *predictive* validity, make it ideal for the screening of potential neuroprotective therapies for the treatment of PD.

In conclusion this BSSG toxic model has many if not all of the characteristics of human idiopathic PD. So closely does this model appear to follow human PD that it is tempting to speculate that an understanding of this model may contribute significantly to our understanding of the etiology of idiopathic PD.

Reference

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