Shedding light on early Parkinson's disease pathology

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In a mouse model of early Parkinson's disease (PD), animals displayed movement deficits, loss of tyrosine-hydroxylase (TH)-positive fibers in the striatum, and astro-gliosis and micro-gliosis in the substantia nigra (SN), without the loss of nigral dopaminergic neurons. These findings, which may cast light on the molecular processes involved in the initial stages of PD, are available in the current issue of *Restorative Neurology and Neuroscience*.

"The most intriguing finding of our study was the lack of a significant decrease of TH levels in the SN of the low-dose MPTP-treated mice, suggesting that this treatment does not induce a direct loss of nigral dopaminergic neurons," says Joost Verhaagen PhD, lead investigator of the study. "These findings appear to support the 'dying back' hypothesis of PD, which proposes that the TH-positive terminal loss in the striatum is the first neurodegenerative event in PD, which later induces neuronal degeneration in the SN." Dr. Verhaagen is Head of the Workgroup on Neuroregeneration at the Netherlands Institute for Neuroscience and Professor at the Free University in Amsterdam.

The neurotoxin MPTP (1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine) was used to induce the degenerative changes. Chronic 5 week administration of 25 mg/kg MPTP combined with probenecid (250 mg/kg), which inhibits MPTP clearance and promotes its crossing of the blood-brain barrier, is known to cause dopaminergic neuron degeneration in the SN and decrease striatal dopaminergic nerve terminals. In the current study, 7 mice were treated with 25 mg/kg

MPTP plus probenecid, 6 mice received a lower dose of MPTP (15 mg/kg) plus probenecid, and 8 control mice received saline plus probenecid. A grid test, known to be sensitive to striatal dopaminergic input, was used to detect motor deficits.

Immunohistochemical analysis using TH fluorescence revealed that only the higher dose of MPTP produced significant dopaminergic neuronal cell loss in the SN (65% fluorescence loss, p