NEURODEGENERATIVE DISEASE

New leads for Parkinson's disease

The causes of most cases of Parkinson's disease, which is characterized by loss of dopaminergic neurons in the substantia nigra, are unknown. However, ~10% of cases have been linked to mutations in specific genes, particularly the gene encoding leucine-rich repeat kinase 2 (LRRK2). *In vitro* studies have also suggested a role for mutant forms of LRRK2 in neurotoxicity. Now, Lee *et al.* have investigated the importance of these findings *in vivo* and identified LRRK2 kinase inhibitors that reduce neurotoxicity in mice, highlighting this approach as a potential therapeutic strategy for Parkinson's disease cases that are linked to LRRK2 mutations.

First, the authors screened 84 known kinase and phosphatase inhibitors in an *in vitro* assay monitoring LRRK2 autophosphorylation. Eight compounds were identified as inhibitors of LRRK2 kinase activity, each with approximately equal potency against the wild-type enzyme and a mutated version (G2019S) that is a common cause of familial and sporadic Parkinson's disease. From these compounds, the indolinones GW5074 and indirubin-3′-monooxime were selected for further study as they are known to cross the blood–brain barrier.

In primary cortical cells *in vitro*, overexpression of the mutant LRRK2 led to neuronal injury and cell death. These effects were attenuated by the two study compounds and also by the multi-kinase inhibitor sorafenib, which, like GW5074, inhibits Raf — another kinase related to LRRK2. Other kinase inhibitors that do not block LRRK2 kinase activity were unable to prevent the cell injury and death caused by overexpression of mutated LRRK2, further supporting this enzyme as the target of the neuroprotective compounds.

To determine the efficacy of the LRRK2 kinase inhibitors *in vivo*, the authors used a fluorescently tagged viral amplicon construct to deliver the mutant form of the enzyme into the striatum of mice through intracranial injection, thereby creating a model of Parkinson's disease. The resultant overexpression of mutant LRRK2 caused a significant loss of dopaminergic neurons in the substantia nigra (identified by expression of tyrosine hydroxylase, an enzyme involved in the production of dopamine). By contrast, overexpression of wild-type LRRK2 or a kinase-dead form of the mutant enzyme did not have adverse effects. Twice-daily intraperitoneal injections of GW5074 or indirubin-3′-monooxime for 3 weeks attenuated the loss of tyrosine hydroxylase-positive neurons caused by overexpression of the mutant LRRK2.

Together, these findings highlight the therapeutic potential and feasibility of targeting aberrant LRRK2 kinase activity in Parkinson's disease, and could provide a model to address other genetic mutations that have been associated with this disorder.

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ORIGINAL RESEARCH PAPER Lee, B. D. *et al.* Inhibitors of leucine-rich repeat kinase-2 protect against models of Parkinson's disease. *Nature Med.* **16**, 998–1000 (2010)