MedicalXpress

Blocking LRRK2 activity is not a simple answer to Parkinson's disease

May 29 2012

Mutations in the LRRK2 gene are the most common cause of genetic Parkinson's disease (PD). New research published in BioMed Central's open access journal *Molecular Neurodegeneration* demonstrates that loss of function of LRRK2 (by deletion of the kinase domain) leads to changes in motor co-ordination and causes anxiety-like behaviors and kidney degeneration in mice without affecting dopamine-mediated brain activity.

The protein LRRK2 is involved in regulating the structure and function of neurons. Aberrant LRRK2 has been shown experimentally to have subtle effects on dopamine signaling which may mirror the earliest changes in PD patients. In order to investigate how LRRK2 works researchers from Mayo Clinic deleted the kinase domain of LRRK2 protein in mice.

Dr Heather Melrose, who lead this study explained, "Since the gene is too big to delete the entire gene we targeted the kinase domain because we regarded this as the most important functional region. The specific section we deleted, exon 41, encodes the activation hinge of the kinase. The experimental strategy actually resulted, as we hoped, in a complete loss of the LRRK2 protein in the mice."

The team found that loss of LRRK2 did not affect dopamine signaling in the mice. The mice appeared to be normal however they had subtle behavioral changes similar to those previously seen for mice with the LRRK2 mutation G2019S, and sometimes seen in PD patients, such as

increased anxiety. Deletion of the LRRK2 protein also affected kidney function.

Dr Melrose continued, "The most common mutation of LRRK2 (G2019S) is within the kinase domain however it is not thought to lead to a loss in kinase activity. Instead it is thought that the mutated LRRK2 kinase is somehow 'toxic' and anti-LRRK2 therapies are currently being designed to lower LRRK2 levels or block its kinase activity. Our results suggest that blocking normal LRRK2 activity causes emotional behavior changes in mice. These changes may be similar to anxiety disorder in PD, a disabling non-motor symptom of the disease which often precedes the motor defects by decades. Our data adds evidence to a different theory, that some biological consequences of the LRRK2 mutations may be a loss rather than gain of function."

It seems then that LRRK2 is a complicated protein and that restoring normal activity to patients with PD is not going to be simple. Not only may anti-LRRK2 therapies have side effects on the kidney but they also may disrupt some brain functions and sensory processing. These are going to be important considerations for design and use of LRRK2-based therapeutics.

More information: LRRK2 knockout mice have an intact dopaminergic system but display alterations in exploratory and motor co-ordination behaviors
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Molecular Neurodegeneration (in press)