LRRK2 kinase activity modulates presynaptic vesicle release

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Mutations in Leucine-rich repeat kinase 2 (LRRK2) are the single most common cause of inherited Parkinson´s disease (PD). Little is known about its involvement in the pathogenesis of PD mainly due to the lack of knowledge about the physiological role of LRRK2. Our previous results suggest that LRRK2 acts as a scaffold within the presynaptic bouton and that it is involved in neurotransmitter release acting on synaptic vesicle (SV) trafficking trough the interaction with actin cytoskeleton and SNARE proteins. Besides containing just protein-protein interactions modules, such as the amino-terminal leucine-rich repeat domain and the carboxy-terminal WD40 domain, LRRK2 also contains an active kinase domain. The complex network of presynaptic proteins regulating SV cycle is finely modulated by post-translational modifications (PTM), in particular by phosphorylation, thus it is tempting to speculate that LRRK2 kinase activity might controls SV trafficking. To this aim, we have analysed the impact of LRRK2 kinase inhibition by combining electrophysiological, biochemical and imaging approaches. Our results indicate that LRRK2 kinase activity modulates presynaptic release, LRRK2 binding to SV and influences SNARE complex stability. In order to elucidate the molecular mechanisms linking LRRK2 with the presynaptic machinery, we have tested if LRRK2 can phosphorylate its presynaptic partners. We have focused on two major phosphoproteins enriched at the presynaptic bouton, NSF and Synapsin I/II. We have found that LRRK2 phosphorylates NSF and Synapsin I in vitro. Since NSF and Synapsin I regulate respectively the disassembly of the SNARE complex and SV tethering to the actin cytoskeleton, our data bring evidence to the implication of LRRK2 phosphorylation in SV trafficking. Robust literature demonstrated that the main pathological mutation G2019S brings to an increase of LRRK2 kinase activity. Given the presynaptic alterations seen in LRRK2 disease model, we hypothesise that LRRK2 is a pivotal regulator of SV cycle and that presynaptic SV release represents a pathological target in PD.

References:

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