Mutations in the leucine-rich repeat kinase-2 (LRRK2) gene cause late-onset Parkinson’s disease, but the physiological function of LRRK2 is largely unknown. Here we report that LRRK2 impairs basal macroautophagy in cultured cells. LRRK2 overexpression does not impair autophagy activation, but autophagic degradation due to an increase in lysosomal pH. This results in decreased cell survival in the presence of lysosomal inhibitors or protein aggregation-induced stress. Simultaneously, LRRK2 enhances autophagosome formation through a calcium-dependent protein kinase kinase-β (CaMKK-β)/AMP-dependent protein kinase (AMPK) pathway, which can be inhibited by calcium chelation or ectopic Bcl-2. The LRRK2-mediated deregulation of macroautophagy involves activation of nicotinic acid adenine dinucleotide phosphate (NAADP)-sensitive two-pore channels (TPCs) located on acidic stores, and can be blocked by a specific antagonist. Collectively, our data indicate a molecular mechanism for LRRK2 deregulation of autophagic degradation and reveal previously unidentified therapeutic targets.