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Genetic modulation of PINK1 differentially affects mitophagy compared with autophagy disclosing common mechanisms of genetic and environmental parkinsonism

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The second most frequent cause of autosomal recessive Parkinson's disease is represented by mutations in the PTEN-induced putative kinase1 (PINK1). The PINK1 protein mainly localizes to mitochondria which are considered the target organelles mainly affected in Parkinson's disease. In fact, parkinsonism-inducing neurotoxins such as rotenone, MPTP and methamphetamine all damage mitochondria. Therefore, the ability to counteract mitochondrial toxicity and promoting mitochondrial renewal by mithophagy and mitochondrial biogenesis is critical to cure Parkinsonism. For instance the autophagy-dependent removal of altered mitochondria known as mitophagy is supposed to be key in conteracting mitochondrial toxicity. Interestingly mitochondrial PINK1 is known to interact with autophagy proteins such as beclin1 and the ubiquitin-ligase parkin. Therefore, in the present study we evaluated whether such an interaction produced downstream effects leading to autophagy activation. This was evaluated through the simultaneous analysis of co-localization of parkin and beclin1 with the autophagy initiator ubiquitin. These phenomena were analyzed both at mitochondrial level and throughout the cytosol by analyzing autophagy-like vacuoles and LC3-II positive structures. Interestingly, despite increased mitophagy PINK1 overexpression did not produce a general activation of the autophagy pathway. It is likely that such a selective fashion of autophagy activation only limited to mitochondrial removal could explain the relevance of PINK1 for Parkinson's disease but not for other neurodegenerative, autophagy-related disorders. The present data were obtained through several experimental settings featuring PINK1 overexpression, mutation, deletion and silencing of the gene. The effects were analyzed in baseline conditions but were supplemented by experiments in the presence of methamphetamine used here both as a mitochondrial neurotoxin and an autophagy-dependent Parkinsonism inducing compound. Data revealed that PINK1 was critical for mitochondria and cell viability already in baseline conditions though such an effect was magnified upon methamphetamine exposure. The present findings while explaining the molecular interactions which are likely to induce PINK1-dependent genetic Parkinsonism, provide a further evidence on the critical role of genetic and environmental alterations in the genesis of Parkinson's disease.

Keywords: PINK1, Parkinson's disease, methamphetamine, mitophagy.