The Missing Link: Parkin as a Mediator of Alpha-Synuclein-Induced Behavioral Changes

Anna Wilkaniec [1]*, Grzegorz A. Czapski [1], Gabriela Olech-Kochańczyk [1], Elżbieta Gawinek [1], Magdalena Cieślik [1], Ewelina Bielska [1], Piotr Wójcik [1], Urszula Czyżewska [2], Magdalena Czerniecka [2], Adam Tylicki [2], Agata Adamczyk [1].

1. Department of Cellular Signalling, Mossakowski Medical Research Institute, Polish Academy of Sciences, Pawińskego 5, 02-106 Warsaw, Poland.
2. Faculty of Biology, Department of Microbiology and Biotechnology, Laboratory of Cytobiochemistry, University of Białystok, Ciołkowskiego 1J, 15-245 Białystok, Poland.

Parkin regulates mitochondrial quality control and redox homeostasis, but its role in the brain response to alpha-synuclein (a-Syn) remains unclear. We investigated whether Parkin modulates behavioural, oxidative, and metabolic consequences of a-Syn oligomer administration.

Adult wild-type (WT) and Prkn knockout (KO) mice received bilateral intrastriatal injections of soluble a-Syn oligomers or vehicle and were followed for 180 days. Longitudinal behavioural profiling assessed spontaneous and exploratory activity, motor strength, coordination, grooming, anxiety-related behaviour, and object recognition. To define the underlying biochemical response, oxidative and nitrosative stress were assessed in the cerebral cortex, hippocampus, striatum, and midbrain at 30, 90, and 180 days post-injection using complementary measures of reactive oxygen species, superoxide/redox status, and NADPH oxidase (NOX) activity. In parallel, lactate dehydrogenase (LDH), glucose-6-phosphate dehydrogenase (G6PD), and malate dehydrogenase (MDH) activities were analysed to probe alterations in energy metabolism and NADPH/redox homeostasis.

In WT mice, a-Syn oligomers induced a dynamic, region- and time-dependent biochemical response. Early alterations in cortical, hippocampal, and striatal redox parameters were followed by a delayed and sustained oxidative response in the midbrain. These changes were accompanied by progressive functional impairment. At 180 days, a-Syn-treated WT mice showed reduced rearing, exploratory activity, and grip strength, together with alterations in grooming, central-zone behaviour, and object recognition, indicating both motor and non-motor dysfunction.

Strikingly, most of these behavioural abnormalities were absent or markedly attenuated in Prkn KO mice. This protection was not associated with a uniform reduction in oxidative stress. Instead, Parkin deficiency markedly altered the temporal and region-specific redox response to a-Syn. Changes in LDH, G6PD, and MDH activities further demonstrated genotype-dependent alterations in metabolic and redox pathways, suggesting that metabolic adaptation may contribute to the divergent response to a-Syn.

Collectively, our findings challenge the conventional view of Parkin as uniformly protective in alpha-synucleinopathy. Unexpectedly, loss of Parkin attenuated the functional consequences of a-Syn oligomers, challenging the view of Parkin as uniformly protective. These results point to a more complex role of Parkin in linking mitochondrial quality control, metabolic adaptation, redox homeostasis, and the functional consequences of a-Syn pathology.

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