Involvement of Cofilin-1 in Apoptotic Response to 6-Hydroxydopamine – An in Vitro Study of the Pathophysiology of Parkinson’s Disease

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Introduction: The molecular mechanisms underlying neurodegeneration of the nigrostriatal pathway during the progression of Parkinson’s disease (PD) has not been completely understood. Mitochondrial dysfunction and oxidative stress have been strongly related to the pathogenesis of PD and it is known that oxidation of cofilin-1 mediates this events in tumor cells by oxidants (Klamt, et al. Nature Cell Biol, 2009) and could made a role in neuronal cell death when it is induced by neurotoxins, such as 6-hydroxydopamine (6-OHDA). Our aim is to establish the role of cofilin-1 as an inducer of cell death, using the SH-SY5Y cells line following a protocol of differentiation into a dopaminergic neuron-like cells. It was triggered by adding 10 µM retinoic acid and lowering fetal bovine serum from 10%, to maintain the proliferative cells, to 1% for 7 days. (Lopes et al, Brain Res 1337: 85, 2010). Methodology and Results: After we established the 50% of lethal dose value (LD$_{50}$) by MTT assay, we have found increased production of reactive oxygen species in presence of 6-OHDA. Time course experiments following 6-OHDA treatment showed that cofilin-1 translocates from the cytosol to the mitochondrial fraction before any signal of mitochondrial dysfunction (loss of ΔΨm and cytochrome c release), caspases activation and morphological markers of apoptosis appeared. Differentiated SH-SY5Y cells transfected and overexpressing a plasmid containing CFL1 cDNA showed higher susceptibility to 6-OHDA neurotoxicity. Conclusions: Thereby, we found that treatment of dopaminergic neuron-like cells with 6-hydroxydopamine induces ROS production and cofilin-1 translocation to mitochondria before the organelle dysfunction and caspase-9 activation. SH-SY5Y cells transfected with CFL1 gene are more susceptible to 6-OHDA neurotoxicity, and our data strongly suggest that cofilin-1 play a role in the neurotoxicity caused by 6-OHDA and can be a target for therapeutic studies.

Word Keys: 6-hydroxydopamine, cofilin-1, mitochondrial dysfunction, Parkinson’s disease, SH-SY5Y.

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