DJ-1 PROTECTS AGAINST NEUROTOXIN-INDUCED INHIBITION OF THE PI3K/AKT PATHWAY IN A MODEL OF MESENCEPHALIC NEURONS

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Introduction: Mutations in several genes, including DJ-1, have been associated with early onset cases of Parkinson Disease (PD). DJ-1 has been described to have neuroprotective effects against diverse neurotoxins. However, the impact of DJ-1 on intracellular signaling pathways are not completely clear, in particular its effects on neuronal survival pathways.

Aims: To analyzed the impact of DJ-1 on the PI3K/AKT neuronal survival pathway upon exposure to neurotoxins (C2-ceramide, 6-hidroxidopamine and rotenone).

Methods: We use a model of cathecolaminergic neurons of murine origin (CAD cells). CAD cell survival was analyzed by MTT and LDH assays. CAD cells were transiently transfected to overexpress human wild type DJ-1 (WT-DJ-1) or empty vector (EV) and latter expose to neurotoxins. The total and phosphorylated (Ser473) forms of AKT was analyzed by western blotting.

Results: We demonstrated that these neurotoxins induce CAD death cell in a dose-time dependent manner and was associated to inhibition of the PI3K/AKT pathway. When CAD cells overexpressing WT-DJ-1 were treated with LD50 of the different neurotoxins, the inhibition of the PI3K/AKT pathway was reverted (present higher level of phosphorylated AKT compared to cells transfected with the EV) in cells treated with C2-Ceramide and 6-OHDA, but not in cells treated with rotenone.

Conclusions: DJ-1 reverts the C2-ceramide and 6-OHDA-induced inhibition of the PI3K/AKT pathway in CAD cells, providing a plausible role of DJ-1 as a neuroprotective target for PD.

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