INDUCTION OF THE UNFOLDED PROTEIN RESPONSE BY A-SYNUCLEIN IN EXPERIMENTAL MODELS OF PARKINSON DISEASE

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Introduction: Parkinson disease (PD) is characterized by the accumulation α-synuclein in Lewy bodies. It was shown that an endoplasmic reticulum (ER) stress-related pathway, the unfolded protein response (UPR) is activated in dopaminergic neurons bearing α-synuclein inclusions in the PD brain. Thus, the activation of the UPR may be related to α-synuclein. The UPR is induced by the accumulation of misfolded proteins within the ER. These are bound by the UPR sensor glucose regulated protein/immunoglobulin heavy chain binding protein (GRP78/BiP), which in turn dissociates from and activates three ER stress receptors mediating the UPR. Among these latters, pancreatic (PKR)-like ER kinase (PERK) drives a cascade of events leading to the production of activating transcription factor 4/cAMP responsive element 2 (ATF4/CREB-2) which induces the transcription of genes involved in ER homeostasis, stress-induced apoptosis, and autophagy.

Aims: To evaluate whether the accumulation of α-synuclein within the ER triggers the activation of the UPR and whether this activation coincides with the induction of pro-apoptotic events.

Methods: The expression of GRP78/BiP and ATF4/CREB-2 in “in vitro” and “in vivo” models of PD showing α-synuclein accumulation was studied by western blot, RT-PCR, immunocyto- and immunohistochemistry.

Results: We found that GRP78/BiP was bound to α-synuclein and was increased in “in vitro” and “in vivo” models showing α-synuclein accumulation. In parallel ATF4/CREB-2 was induced.

Conclusions: Our findings indicate that accumulation of α-synuclein within the ER activates the PERK-dependent pathway of the UPR leading to the induction of ATF4/CREB-2. Activation of the UPR may in turn induce pro-apoptotic events.