REGULATION OF A PLASMA MEMBRANE VOLTAGE-DEPENDENT ANION CHANNEL (PL-VDAC) BY ESTROGENS IS RELATED TO THE PATHOGENESIS OF ALZHEIMER’S DISEASE

R. Marin¹, J.L. Herrera¹, C.E. Fernandez¹, M. Diaz²

¹Physiology, ²Animal Biology, La Laguna University, La Laguna, Spain

VDAC is a highly conserved mitochondrial porin which provides a main transport of molecules regulating redox homeostasis and apoptosis. VDAC has also been found associated with the plasma membrane and in lipid rafts (pl-VDAC), where the channel has been suggested to be part of extrinsic apoptosis. Recently, we have provided some evidences supporting that VDAC plays an important role in the pathogenesis of AD, using immunochemical and immunoblotting assays. We have demonstrated in cultured neurons that antibodies directed against human VDAC1 can prevent beta amyloid-induced neurotoxicity. Furthermore, a high VDAC accumulation occurs in the dystrophic neurites surrounding beta amyloid plaques in AD brains, and this channel has been shown to accumulate in lipid rafts of human cortex and hippocampus with AD pathology. In neuronal lipid rafts from cellular and murine models as well as in human cortex, pl-VDAC is associated with estrogen receptor alpha (ER), and this complex appears disrupted in dystrophic neurites of amyloid beta plaques, probably facilitating beta amyloid-mediated cell damage. The porin is constitutively phosphorylated in neuronal membranes, and physiological doses of estradiol, known to neuroprotect against amyloid beta (Abeta) toxicity, enhance its level of phosphorylation through the activation of Src kinase pathways. These data may contribute to understand VDAC regulation related to membrane dysfunctioning events occurring in Alzheimer’s disease (AD), and may also help to decipher the strategies developed by estrogens in neuronal preservation.

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