CELLULAR STRESS RESPONSE, UNCOUPLING PROTEINS AND OXIDATIVE STRESS IN AGEING AND DEMENTIA

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Aims: Alzheimer's Disease (AD) is a neurodegenerative disorder affecting up to one third of individuals reaching the age of 80. AD is neurological disease sharing production of abnormal proteins, mitochondrial dysfunction and oxidative stress, which contribute to the pathogenesis of this so called “protein conformational disease”. The central nervous system has evolved the conserved mechanism of unfolded protein response to cope with the accumulation of misfolded proteins. Several conditions including protein, lipid or glucose oxidation disrupt redox homeostasis and lead to accumulation of unfolded or misfolded proteins in the aging brain. Different integrated responses exist in the brain to detect oxidative stress which is controlled by several genes termed vitagenes. Vitagenes encode for cytoprotective heat shock proteins (Hsp), as well as thioredoxin, sirtuins and uncouple proteins (UCPs). SIRT-1 has been directly implicated in neuronal protection against stress in cultured cells. Uncoupling proteins (UCPs) are a family of mitochondrial membrane proteins that uncouple electron transport from ATP production by transporting protons across the inner membrane. Uncoupling proteins UCP1 is found only in brown fat mitochondria of mammals.

In the present study we evaluated stress response mechanisms in plasma and lymphocytes of control patients compared to AD patients, in order to provide evidence of an imbalance of oxidant/antioxidant mechanisms and oxidative damage in AD patients.

Results: We found that the levels of Sirt-1 and Sirt-2 in AD lymphocytes were significantly higher than in control patients. Interestingly, analysis of plasma showed in AD patients increased expression of Trx, a finding associated with reduced expression of UCP1, as compared to control group.

Innovation and conclusion: These findings open up new neuroprotective strategies, as molecules inducing this defense mechanism can be a therapeutic target to minimize the deleterious consequences associated with accumulation of conformationally aberrant proteins to oxidative stress, such as in neurodegenerative disorders and brain aging, with resulting prolongation of a healthy lifespan.