Mitochondrial Uncoupling Proteins (UCPs): Implications for Neuroprotection in Parkinson's Disease

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The link between mitochondrial dysfunction and neurodegenerative disorders such as Parkinson's disease (PD) remains unclear. The mitochondria provide energy (ATP) to the cell through oxidative phosphorylation, fundamental to all aspects of life. Oxidative phosphorylation uses cellular substrates to generate mitochondrial membrane potential, and hence ATP. It also handles cellular oxygen uptake, producing either water, or reactive oxygen species (ROS) as byproducts. Cellular antioxidant systems neutralize excessive ROS production and oxidative stress. Uncontrolled oxidative stress, ATP deficiency and mitochondrial dysfunction are found in many neurodegenerative disorders, including PD. ROS and ATP production in mitochondria are inextricably linked; this crucial link may lie with UCPs. They uncouple oxidative phosphorylation by dissipating mitochondrial membrane potential and hence reduce ATP production, to generate heat. Partial uncoupling and heat generation are important for normal metabolism. Of the 5 forms (UCP1 to 5), UCP2, 4 and 5 are expressed in neurons. How mitochondrial dysfunction, oxidative stress and ATP deficiency are interlinked and what roles do UCPs play in these processes are unknown. UCP2 can alter ROS and ATP production, and appears to be neuroprotective in oxidative stress. Mitochondria may have evolved mechanisms to regulate ROS formation through UCP expression. Oxidative stress and ATP deficiency may trigger cell responses to reduce cell damage via cooperative responses in UCPs expression. The subcellular localization of UCP5 was different from UCP2, suggesting that UCPs may have different roles in handling ATP deficiency and oxidative stress. Oxidative stress in our PD neuronal model can alter UCP expression, but in different ways. UCP5 expression knockdown can affect mitochondrial membrane potential and increase susceptibility of the neuronal cells to oxidative damage. Understanding the role of neuronal UCPs in mitochondrial dysfunction is an important step in formulating neuroprotective strategies to reduce or prevent cell death in neurodegenerative disorders such as PD.