Mitochondrial metabolism and endogenous antioxidants under NRF2 activation in the mechanism of neuroprotection in neurodegenerative disorders and epilepsy

Andrey Y. Abramov

Department of Clinical and Movement Neurosciences, UCL Queens Square Institute of Neurology, Queen Square, London, UK

Email: a.abramov@ucl.ac.uk

Most of the neurodegenerative disorders and some of neurological conditions such a epilepsy characterised by mitochondrial disfunction which results in energy deprivation and oxidative stress and neuronal loss. Nrf2 controls major endogenous antioxidant pathways and also support mitochondrial metabolism by substrates. We have found that pharmacological activation of Nrf2 restore energy metabolism and increase the level of GSH in the familial forms of Parkinson's disease (PINK1 and SNCA triplications) and protect neurons against cell death. In epilepsy, KEAP1 inhibition (activation of Nrf2) is neuroprotective and suppresses the development of seizures. However, the most effective treatment of the epilepsy was the combination of the Nrf2 activation (pharmacological Keap1 inhibition) and inhibitor of NADPH oxidase. Importantly, this combination completely restore altered mitochondrial membrane potential, decrease seizure-induced ROS production and prevented the development of spontaneous seizures. Thus, Nrf2 is one of the most promising target for treatment of the neurodegenerative disorders and epilepsy.

Andrey Y. Abramov is a Professor at the Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology. He studies the role of mitochondria, calcium signalling and redox biology in physiology of the Central nervous system and in the mechanism of the pathology of neurodegenerative disorders. In the last decade in collaboration with Professor Dinkova-Kostova we identified novel and underestimated role of Nrf2 in mitochondrial bioenergetics