Title of project: Oxidative metabolism adaptation to Coenzyme Q deficiency in the brain; effect of statins

Statins, the most widely prescribed medications worldwide, are cholesterol-lowering drugs that effectively reduce the risk of major cardiovascular events by blocking a key enzyme in the mevalonate pathway, which is responsible for the biosynthesis of Coenzyme Q (Q).

Mitochondrial Q (mQ) is inevitable in the proper functioning of the electron transport chain and energy production. mQ also participates in the production of reactive oxygen species (ROS) by respiratory chain. On the other hand, Q is a potent intracellular antioxidant present in all membranes in the cell. A significant loss of mQ can lead to a decrease in mitochondrial activity and a gradual development of lesions. Oxidative metabolism, of which mitochondria and mQ are key elements, meets the high energy needs of the brain. Brain dysfunction can be related to brain mitochondrial dysfunction, including increased mitochondrial ROS (mROS) formation.

We hypothesize that statins affect the bioenergetic functioning of mitochondria in the brain, leading to a metabolic response associated with lowering mQ levels. We will study whether this response is associated with respiratory chain inhibition and increased mROS production, especially in the brains of older animals with already physiologically reduced mQ levels.

The purpose of this project is to elucidate the effect of hydrophobic statins crossing the blood-brain barrier, used at physiological concentrations, on the aerobic metabolism of brain cells in relation to changes in mitochondrial function. We propose the multi-level approach to studying the effect of two popular cholesterol-lowering statins, simvastatin and atorvastatin, on brain oxidative metabolism, i.e. at the level of (i) *in vitro* statin-exposed astrocytes, and mitochondria isolated from them, (ii) isolated rat cerebral cortex mitochondria treated with statins (study on the direct effect of statins on brain mitochondria), and (iii) rat cerebral cortex cells and their mitochondria derived from animals treated with statins. In animal studies, we will compare statin-induced changes in bioenergetic activity of mitochondria from brains of young (3-month-old) and middle-aged (12-month-old) male rats, which differ physiologically by the amount of Q and mQ.

The lack of research combining statin therapy and mitochondrial adaptation (dysfunction?) of brain cells, in the face of such widespread statin treatment in modern times, supports undertaking planned research. One compelling reason to focus on the effect of statins on mitochondrial function in the brain is the essential role of Q homeostasis in this highly energy-dependent organ. Importantly, the brain compared to other organs with a high energy demand has a significantly smaller amount of cellular Q and mQ, hence it is more susceptible to statin-induced deficiency of this important antioxidant and electron carrier. Statin-induced alterations in Q homeostasis leading to mitochondrial dysfunction and oxidative stress can cause pathophysiological conditions, especially with age. Antioxidant Q10 therapy may alleviate these mROS-related brain disorders. It is therefore important to elucidate the effect of statins on the bioenergetic functioning of mitochondria in the brain, which leads to a metabolic response associated with lowering mQ levels. Our studies will answer how statin-treated brain cells cope with oxidative stress, and how important mQ and mitochondrial energy-dissipating systems are in this phenomenon.

Since statins are widely used, awareness regarding their potential side-effects would lead to better treatment. Because mitochondria are a potential site of pharmacological intervention aimed at broadly understood cell protection under conditions of oxidative stress, these studies may be helpful in the long term in verifying or supplementing existing statin and other Q-related therapies.