,, Mitofusin 2 role in cell death and survival in brain ischemia-reperfusion models.”

Proper mitochondrial functioning is crucial for the neuron and, under conditions of ischemia and reperfusion (I/R) can determine its survival or death. The activity of mitochondria depends on many processes, among which the phenomena of fusion and fission of mitochondria and elimination of damaged organelles by autophagy play a crucial role. These processes might prevent the accumulation of damaged mitochondria and support the maintenance of proper mitochondrial morphology and function. On the other hand, the loss of mitochondria can be supplemented by mitochondrial biogenesis. However, the precise role of these processes in the survival of the neuron after I/R and the relationships between them are not fully understood.

It has been hypothesized that mitofusin 2 (Mfn2), a protein involved in mitochondrial fusion, might integrate mitochondrial network remodeling with mitophagy and mitochondrial biogenesis in post-ischemic neurons. Therefore, the main aim of this study was to investigate the role of Mfn2 in the neuronal response to ischemia-reperfusion injury, with particular focus on the mitochondrial network dynamics, mitochondrial content and quality.

Two experimental models were used. An *in vivo* studies were performed in the model of transient cerebral ischemia followed by reperfusion (I/R) in mongolian gerbils. Two areas of the hippocampus: ischemia-vulnerable (CA1) and ischemia-resistant (CA2-3, DG) were analyzed. Secondly, a primary culture of rat cortical neurons, wild type and Mfn2-knock down, were subjected to transient oxygen and glucose deprivation.

It was shown that in the CA2-3, DG neurons and wild-type neurons *in vitro*, post-ischemic damage of the mitochondria is initially repaired by the enhanced dynamics of the mitochondrial network. An increase in mitochondrial fusion and in mitochondrial elimination at later stage of reoxygenation have been observed. Furthermore, the activation of the mitochondrial biogenesis and subsequent increase in the amount of respiratory complexes proteins has been shown. Meanwhile, the content of Mfn2 increased significantly.

On the other hand, the reduction of the Mfn2 protein level, as observed in CA1 after I/R and induced in Mfn2-knock down neurons, promotes a significant fragmentation of mitochondria. In CA1 neurons after I/R episode and in Mfn2-knock down neurons after OGD mitochondrial damage was significantly enhanced. An increased mitochondrial fusion was not observed. In

parallel, an increased macroautophagy has been demonstrated shortly after the insult. In contrast to the hippocampal CA2-3, DG *in vivo* and wild-type neurons *in vitro*, activation of mitochondrial biogenesis was not observed. This type of cellular response is not neuroprotective and, as a result, CA1 neurons *in vivo* undergo delayed degeneration.

Thus, presented results suggest that Mfn2 is one of the key proteins conditioning pro-survival response of neurons to transient ischemic injury, enabling their survival, by regulating the relationship between mitochondrial elimination and biogenesis. These phenomena might contribute to the mechanism of the endogenous neuroprotection observed in CA2-3, DG and promote neuronal survival in these areas of the hippocampus.