

ROLE OF ARGINASE 2 IN THE FUNCTION OF THE STRIATUM AND IN THE PATHOGENESIS OF HUNTINGTON'S DISEASE

Each individual cell in the body requires specific set of chemical compounds to support its physiological requirements. Majority of these compounds are produced by the cells themselves in the series of sequential chemical transformations that constitute metabolic pathways and are controlled by specific enzymes. Disturbances in cellular metabolism caused by either internal or external factor (for example genetic mutation or toxic exposure, respectively) may affect cell function and may significantly contribute to the development of various disorders. Indeed, metabolic alterations accompany virtually all diseases, however, the involvement of these alterations in the pathogenesis is often not known.

Impairment in metabolic pathway of arginine, a versatile amino acid that may be involved in energy production, cellular signalling or transmission of neuronal signals, is often reported in Huntington's disease, an inherited, incurable and fatal brain disorder. Huntington's disease is characterized by progressive movement deficits, emotional impairment and memory difficulties, symptoms that arise from progressive neuronal death in the brain, primarily in the striatum, a structure lying deep under the cortex, that is affected the most in the course of the disease. Arginine was shown to be increased and its product, ornithine - decreased in Huntington's disease patients and experimental models. It was also shown experimentally, that high levels of arginine in the food significantly accelerates the disease symptoms in the mouse models of Huntington's disease, suggesting direct involvement of arginine in the mechanisms leading to the disorder.

Consistent with metabolite alterations, I recently reported an impairment of arginase, an enzyme controlling conversion of arginine to ornithine, in the striatum of mouse model of Huntington's disease. The deficit was already present at the early stage, before the neurological symptoms are observed in this model, and was progressing with the course of the disease. The role of arginase is well established in the other tissues, especially liver, where this enzyme is involved in removing of ammonia from the body, but its precise function in the brain is not well recognized. It was however shown that neurons that are experimentally enriched with arginase are protected better against death or damage induced by diverse factors. Although its detailed localization is poorly characterized, my preliminary study indicate that arginase is present in just few, strictly defined regions of the brain, with striatum containing the highest levels of this enzyme. Restricted distribution of arginase suggests therefore that this enzyme plays specific role in striatal cells and in other selected types of brain cells, and its early deficit in Huntington's disease, may, through the alterations in local metabolism of arginine, lead to the impairment of the functioning of these cells, contributing to disease progression.

My project is aimed to explain how striatal arginase controls specific functions in the brain, and what are the consequences of arginase deficiency in Huntington's disease. To this end I will employ genetic mouse models of Huntington's disease and of arginase deficit to find how this enzyme or its absence affects the brain at the level of molecules, cells and tissue. Specifically, I will attempt to answer the following questions:

- what is the distribution of arginase in the striatum and what is the role of arginase-dependent metabolism of arginine in the function of this region of the brain?
- what are the changes in arginase in Huntington's disease?
- what are the consequences of arginase deficit for the development of Huntington's disease?

Precise knowledge on striatal arginase distribution and function in the normal and diseased brain will allow to unravel novel, yet unknown properties of selected types of brain cells, helping to better understand the molecular basis of brain functioning, and will benefit our knowledge on the mechanisms involved in development of Huntington's disease, establishing potential targets for novel therapeutic strategies against this and other disorders.