Project title: Modulation of mutant huntingtin level by genistein in the mouse model of Huntington's disease and its effects on psychomotor development of animals

Project objective:

Huntington disease (HD) is a genetically-transmitted, progressive neurodegenerative disease, inherited in an autosomal dominant manner. It is caused by a mutation resulting in expansion of CAG nucleotide triplets in exon 1 of the *IT15* (*HTT*) gene. This mutation results in appearance of a long tract of glutamine residues in the huntingtin (HTT) protein which impairs its proper folding. As a result, mutant huntingtin (mHTT) accumulates in cells, including neurons, as insoluble and hardly removable aggregates which impair functions of these cells. Such dysfunctions lead to various adverse effects in psycho-motoric functions, like changed behavior and impaired cognitive abilities. Quality of life of patients deteriorates in time, and they became dependent on their caregivers. The death occurs usually between 15 and 20 years since diagnosis.

Despite many attempts, no effecvtive drug for HD could be find, and current treatment is restricted to alleviation of some symptoms. Thus, searching for possibilities of HD treatment is of high scientific importance. One of the most promising strategies is enhanced mHTT degradation by cellular organelles called lysosomes. They are able to destroy partially damaged or non-functional macromolecules. This process occurs at a low level in healthy cells, which allows to re-use the monomers for cell metabolism. Enhancement of the degradation reactions may lead to removal of mHTT. However, degradation-stimulating molecules, considered to date, gave also severe adverse effects. Therefore, it is crucial to find a compound that stimulates the process, but at the same time is able to cross the blood-brain-barrier, and if safe for a long-term use.

The compound which can fulfill all these requirements is genistein. It belongs to the group of flavonoids, which occur in various vegetables, particularly in soy. Preliminary studies on a cellular model of HD indicated that genistein stimulates functions of lysosomes and decreases levels of mHTT, causing higher viability of cells. Therefore, the next step in the studies should involve experiments on the animal models of the disease.

What experiments are planned in the project?

In the planned studies, the mouse HD model will be used. Both wild-type and HD mice will be tested in two groups, treated with either water or genistein. General activity of animals will be assessed by using the novelty and open field tests. Motor functions will be estimated in the hanging test and RotaRod. Cognitive abilities will be assessed in the Morris water maze test. Emotional changes will be assessed in the elevated plus maze test. Biochemical, cytological and histological test will be performed in order to evaluate effects of genistein in cells from various organs, particularly the brain and muscles, on: levels of mHTT and HTT, number and size of mHTT aggregates, and induction of the autophagy process.

Why are these studies proposed?

Neurodegenerative diseases, caused by accumulation of toxic proteins, are 4th most often cause of human death, and their number increases, mostly due to the process of ageing of the society. It is estimated that in 2050, the number of patients suffering from these diseases will be over 115 million, which is about 3 times higher than today. Thus, testing mechanisms of action and effects of potential drugs for HD is important to gain basic knowledge that might be further used for development of effective drug against this and other diseases with similar etiology.