ABSTRACT („Morphological characteristics of alterations in the striatum induced by neurodegenerative process in the brain“)

Huntington´s disease (HD) is an inherited neurodegenerative disorder. Although the cause of HD, i.e. the production of the mutant form of unstable protein huntingtin (mhtt) which contains 40 and more CAG repeats is known, the effective therapy is not yet available. Therefore, the use of animal models is crucial for the study of the pathogenesis of this fatal disorder. To date, there is no suitable experimental model simulating the neurodegenerative process (NDP) developing in the striatum of the human HD brain. Most of rodent models of HD fall into two broad categories - the neurotoxic lesions and genetically engineered models.

The primary aim of our study was a comprehensive morphological description of the development of NDP of HD phenotype in the striatum of the rat brain. We compared the progression of NDP in the lesion induced by intrastriatal injection of quinolinic acid (QA) and in rats transgenic for HD. The groups of male rats surviving for 3, 6-7, 14 days, 1, 3, 6, 9 and 12 months after the QA lesion were compared with 2-, 6-, 12-, 18-, 22-24-month-old tgHD rats and age-matched control (intact) counterparts in both groups.

The primary morphological feature of the NDP of HD phenotype is a premature death of striatal neurons, resulting in the progressive striatal atrophy compensated by the dilatation of lateral brain ventricles, followed by the development of the reparative astrogliosis. Intrastriatal injection of the QA into the rat brain induces the progressive NDP, i.e. fast degeneration of the majority of striatal neurons and the development of prominent concomitant astrogliosis with the presence of $GFAP^+$ reactive hypertrophic astrocytes (typical also for NDP in human brain) during the acute phase (3-28 days after the QA lesion). These reactive astrocytes re-express intermediate filaments also typical for immature glial cells (nestin, vimentin). This phenomenon indicates that reactive astrocytes share some attributes with adult stem cells committed for gliogenesis. Despite the slow progression of NDP during the chronic phase (3-12 months after the QA lesion), a massive degeneration of striatal neurons is almost finished and therefore, the reactive astrogliosis declines (in contrast to the progression in human HD).

Although the NDP in the brain of tgHD rats is progressive, its course is rather atypical because of only slow degeneration of striatal neurons. Therefore, the substantial morphological changes appear only in 1-year-old rats. Neurons primarily decrease in size, less are really dying. Neuronal degeneration (like in human HD brain) is selective. The gradual accumulation of polyglutamine (mhtt) aggregates in nuclei of striatal neurons is also typical. Very slow progression of the NDP is not able to induce the conspicious reactive astrogliosis, and neither hypertrophic nor $nestin^+$ and $vimentin^+$ reactive astrocytes are present. The aging changes also contribute to the progression of NDP.

Based on our results, the use of both mentioned models and the combination of findings is suggested to be the most effective in this research field.