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A cytoskeletal perspective on mitochondrial stress in Huntington's disease

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Huntington's chorea is a neurodegenerative autosomal dominant disease characterized by impairment of motor and cognitive functions. The disease is caused by the expansion of CAG trinucleotide repeats in the huntingtin protein gene (HTT), leading to elongation of the polyglutamine N-terminal domain, which stimulates the accumulation of defective globules and subsequent neurodegeneration. The molecular and cellular basis of Huntington's disease pathogenesis is not fully understood and is the subject of active and extensive research. Recent studies have demonstrated the pleiotropic role of mitochondrial fusion and fission proteins and cytoskeletal components in a number of processes including mitochondrial metabolism, redox signaling, mitochondrial DNA maintenance and cell death. The existing evidence suggests a connection between Huntington's disease and mitochondria-associated oxidative stress. Since the precise cytophysiological mechanisms underlying the pathogenesis of Huntington's disease have not yet been discovered, generation of reactive oxygen species and consequent oxidative stress caused by mitochondrial dysfunction associated with huntingtin could be one of the possible explanations.

The aim of this research was to investigate possible changes in the morphological and dynamic parameters of mitochondria in the cells of patients with Huntington's disease, including their branching, intracellular transport and interactions with cytoskeletal components. The cytoskeletal architecture was examined after immunocytochemical staining using wide-field fluorescence microscopy, confocal scanning microscopy, and intravital observations. During the analysis of the results, the following parameters were measured: the number of mobile mitochondria; number of mitochondrial mergers and divisions; the velocity and directionality of intracellular transport; the degree of mitochondrial branching. Obtaining results consistent with data on changes in the dynamics and morphology of mitochondria in other neurodegenerative diseases will allow us to consider not only mitochondria, but also proteins that mediate their connection with the cytoskeleton to be an adequate target for a new type of perspective drugs aimed at preventing the development of Huntington's disease and relief of its symptoms.

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