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Abstracts

S4 Mitochondrial Medicine

Lectures

4L.1 Genotype–phenotype correlation in Leber hereditary optic neuropathy

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Leber hereditary optic neuropathy (LHON), acute or subacute vision loss due to retinal ganglion cell death which in the long run leads to optic nerve atrophy is one of the most widely studied maternally inherited diseases caused by mutations in mitochondrial DNA. Although three common mutations, 11778G>A, 14484T>C or 3460G>A are responsible for over 90% of cases and affect genes encoding complex I subunits of the respiratory chain, their influence on bioenergetic properties of the cell is marginal and cannot fully explain the pathology of the disease. The following chain of events was proposed, based on biochemical and anatomical properties of retinal ganglion cells whose axons form the optic nerve: mitochondrial DNA mutations increase reactive oxygen species production in these sensitive cells, leading to caspase independent apoptosis. As LHON is characterized by low penetrance and sex bias (men are affected about 5 times more frequently than women) the participation of the other factors — genetic and environmental — besides mtDNA mutations was studied. Mitochondrial haplogroups and smoking are some of the factors involved in the complex etiology of this disease. The results of mutation and haplogroup distribution in Polish LHON patients is presented as well as molecular study of lymphoblasts with two mtDNA mutations 3460G>A and 11778G>A.

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4L.2 Defects in mitochondrial oxidative phosphorylation: Role of supercomplexes

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Mitochondrial dysfunction is a major contributor in heart failure (HF). In moderately severe coronary microembolization-induced HF in dogs we reported a decrease in oxidative phosphorylation in cardiac mitochondria due to the decrease in the amount of the supercomplex consisting of complex I/complex III dimer/complex IV. We concluded that the mitochondrial defect in HF lies in the organization of respirasomes. We asked whether this defect in the supramolecular assembly is due to changes in the phospholipids of the mitochondrial inner membrane or modifications of the subunits of the electron transport chain complexes. The contents of the main phospholipid species, including cardiolipin, as well as the molecular species of cardiolipin, were unchanged in cardiac mitochondria in HF. In heart mitochondria isolated from HF complex IV not incorporated into the respirasomes contained an increased content of threonine phosphorylation. This suggested that cyclic AMP may have a role. In saponin-permeabilized heart muscle fibers, cAMP caused a decrease in oxidative phosphorylation, at least at the level of complex IV. We suggest that phosphorylation of specific complex IV subunits either limits the incorporation of complex IV in supercomplexes or decreases supercomplex stability.

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4L.3 Genetic disorders of mitochondrial ATP synthase

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Mitochondrial diseases due to inborn defects of ATP synthase result from mutations in both mitochondrial and nuclear genes. Maternally transmitted dysfunction of ATP synthase is mainly caused by mtDNA missense mutations of varying pathogenicity in the *ATP6* gene. They alter the function of F_O proton channel, result in loss of ATP-synthetic activity and manifest as NARP, MILS or striatal necrosis syndromes. Rarely also *ATP8* mutation or altered splicing of *ATP8–ATP6* transcript is found. A distinct group of inborn defects is represented by ATP synthase deficiency due to nuclear genome mutations. Biochemically, it is characterized by selective inhibition of enzyme biogenesis and patients show generalized ≥70% decrease in the content of ATP synthase. Insufficient ATP synthase phosphorylating capacity results in impaired energy provision and increased ROS production due to elevated level of mitochondrial membrane potential. ATP synthase deficiency appears to be rather frequent, most cases present with neonatal onset, hypotonia, lactic acidosis, hyperammonemia, cardiomyopathy and 3-methylglutaconic aciduria; about half of them die within few months or years. Up to now pathogenic mutations have been found in two genes, both coding for ancillary factors of ATP synthase biogenesis. The first genetic defect was described in *ATPAF2* gene for assembly factor of F_1 subunit a, in a case