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Abstracts

S8 Mitochondria in Neurodegeneration

Lectures

8L.1 Gender-specific regulation of brain mitochondria

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Many neurodegenerative diseases, such as Morbus Parkinson, exhibit a gender-dependency showing a higher incidence in men than women. Most of the neurodegenerative disorders involve either causally or consequently a dysfunction of mitochondria. Therefore, neural mitochondria may demonstrate a gender-specificity with respect to structural and functional characteristics of these organelles during toxic and degenerative processes. The application of 6-OHDA (6-hydroxydopamine) *in vitro* and *in vivo* represents a well accepted experimental model of Parkinson's disease causing Parkinsonian symptoms. Besides the known effects of 6-OHDA on mitochondria and neural survivability, we aimed to demonstrate that the mitochondrial neurotoxin affects the morphology and survival of primary dopaminergic and non-dopaminergic neurons of the mesencephalon in a gender-specific manner by influencing the transcription of mitochondrial genes, ATP and reactive oxygen species production. Our data suggest that cell death in response to 6-OHDA is primarily caused due to increased oxidative stress which is more pronounced in male than in female mesencephalic neurons. Cytochrome *c* oxidase, the terminal enzyme of the respiratory chain, appears to play a crucial role in neuronal cell death and survival. Furthermore, estrogen has been documented as a protective agent in the brain. Recently, mitochondria were shown to be regulated by estrogen influencing ATP and reactive oxygen species production. This makes mitochondria an interesting therapeutic target under neurotoxic and neurodegenerative conditions.

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8L.2 The brain in flames: Mitochondria in inflammatory neurodegeneration

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Inflammatory neurodegeneration is neuronal degeneration due to inflammation, and contributes to most brain pathologies. We have identified three mechanisms by which inflamed glia kill neurons: iNOS, PHOX and phagocytosis. Inflammatory mediators induce the expression in glia of inducible nitric oxide synthase (iNOS). NO inhibits mitochondrial respiration at cytochrome oxidase in competition with oxygen, while NO derivatives peroxynitrite and S-nitrosothiols inactivate mitochondrial complex I, resulting in a stimulation of oxidant production by mitochondria. We find that glial iNOS (or neuronal nNOS) expression induces neuronal death in synergy with hypoxia, basically by NO inhibition of neuronal respiration resulting in glutamate release and excitotoxicity. Acute activation of the phagocyte NADPH oxidase (PHOX) in microglia produces superoxide and hydrogen peroxide, which stimulate microglial production of TNF-α and IL-1β and microglial proliferation. Activation of PHOX together with iNOS produces peroxynitrite, which induces apoptosis of co-cultured neurons. However, inflammatory activation of neuronal–glial co-cultures with LPS or β-amyloid results in progressive loss of neurons (without any apparent cell death) which is accompanied by microglial phagocytosis of neurons, and is prevented by blocking phagocytosis, in culture and *in vivo*.

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8L.3 Mitochondrial DNA, direct repeats, deletions, and centenarians: An unfinished puzzle

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Perfect direct sequence repeats in mitochondrial DNA (mtDNA), and, in particular, the “common” 13 bp repeat, are thought to cause large mtDNA deletions. mtDNA deletions highly progressively accumulate with age and are thought to be actively involved in the aging process. Accordingly, individuals lacking 13 bp repeat are highly prevalent among centenarians. Furthermore, the number of repeats in mammalian mitochondrial genomes in general appears to negatively correlate with species longevity. It is tempting to conclude that the case that mtDNA deletions are significantly involved in the aging process is proven. However, detailed examination of the distribution of mtDNA deletions challenges the role of the 13 bp repeat and other perfect repeats in generating mtDNA deletions. It thus appears that concepts in this field may need to be reconsidered. Comparison of deletional spectra, i.e. the distributions of deletional breakpoints along the mitochondrial genome may be an efficient way of solving this puzzle.

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