Department of Laboratory Medicine

Mitochondrial dysfunction in dopamine neurons
- Implications for Parkinson's disease

AKADEMISK AVHANDLING
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ABSTRACT

Mitochondria are essential for cellular homeostasis and contain the respiratory chain (RC). Decreased mitochondrial function is associated with ageing, as exemplified by the finding of a mosaic pattern of RC-deficient cells in aged tissues. Parkinson's disease (PD) is a common age-related disorder characterized by loss of midbrain dopamine (DA) neurons and formation of intracellular inclusions. A number of observations suggest a role for mitochondrial dysfunction in the pathophysiology of PD: (1) toxins linked to PD have been shown to impair RC function, (2) reduced RC enzyme activities are found in patient tissues, (3) the proportion of DA neurons that are RC-deficient, due to accumulation of mtDNA deletions, is higher in PD patients than in controls, and (4) an inherited form of PD is caused by loss-of-function mutations in the gene for Parkin, an E3 ubiquitin ligase reported to facilitate clearance of defective mitochondria.

In this thesis, experimental genetics in mice have been used to study consequences of mitochondrial dysfunction in the brain, with particular focus on DA neurons. First, we addressed the role of mosaic RC deficiency in the brain by creating chimeric mice with a mixture of normal and RC-deficient forebrain neurons. A low proportion (>20%) of respiratory chain-deficient forebrain neurons was sufficient to cause symptoms. On the one hand, surrounding normal neurons could prevent mortality and delay the onset of symptoms. On the other hand, RC-deficient neurons could induce death of surrounding normal neurons by a trans-neuronal degeneration mechanism.

We also developed so-called 'MitoPark' mice, which have DA-specific disruption of *Tfam*, a gene critical for maintenance and expression of mtDNA. MitoPark mice have severe RC deficiency in DA neurons and develop slow, progressive loss of DA neurons accompanied by motor symptoms resembling those seen in PD. To study changes in mitochondrial morphology and distribution, we developed a novel reporter mouse for cell type-specific labeling of mitochondria. We found that mitochondria in RC-deficient neurons fragmented and concomitantly formed severely enlarged mitochondrial bodies in the soma and proximal dendrites. Mitochondria in distal axon segments had normal morphology, but the RC-deficient neurons had an impaired anterograde supply of new mitochondria to their axon terminals. We did not find support for a role of Parkin in MitoPark DA neurons, as overexpressed Parkin was not recruited to the aberrant mitochondria and the absence of Parkin did not affect their clearance. Finally, we studied the consequences of a complex I defect in DA neurons. Disruption of the complex I subunit gene *Ndufs4* resulted in a mild complex I deficiency, which did not cause degeneration of DA neurons or PD-like symptoms. Nevertheless, we found increased levels of DA metabolites and impaired DA release at the level of the axon terminals, compatible with early changes seen in PD. *Ndufs4* knockout DA neurons were in addition more vulnerable to toxic insult. In summary, these results support a role for mitochondrial dysfunction in PD and show that RC function is important for axonal mitochondrial transport and synaptic DA release.

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