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NEURODEGENERATIVE DISEASE

Synergistic destruction

The pathology of Alzheimer's disease (AD) is characterized by amyloid plaques (aggregates of amyloid-β (Aβ)) and fibrillar tangles (aggregates of tau). Mitochondrial dysfunction has also been recognized as being part of the AD pathology, but the mechanisms underlying this dysfunction are poorly understood. Eckert and colleagues now demonstrate that Aβ and tau synergistically deregulate the mitochondrial oxidative phosphorylation system (OXPHOS).

The authors used quantitative proteomic analysis of the forebrains of 10-month-old wild-type mice, single-transgenic pR5 mice (carrying a neurofibrillary-tangle-forming P301L tau mutation), double-transgenic APP–PS2 mice (which carry mutations in both amyloid precursor protein and presenilin 2 and develop Aβ plaques) and ^{triple}AD (pR5–APP–PS2) mice. They identified 24 proteins that were strongly deregulated in the ^{triple}AD mice. One-third of these were mitochondrial proteins related to complexes I and IV of the OXPHOS.

In accordance with the proteomic findings, the efficiency of the OXPHOS was reduced in cerebral mitochondria isolated from APP–PS2 mice and — to a higher degree — ^{triple}AD mice at 12 months. The mitochondrial function of pR5 mice was not affected at this age, in accordance with previous studies.

Next the authors investigated the activity of complex I and complex IV in isolated mitochondria. Complex I activity in mitochondria from all three transgenic mice was decreased in comparison to in the mitochondria of wild-type mice at 12 months. Complex IV activity in mitochondria from 8-month-old APP–PS2 and ^{triple}AD mice was reduced, and this reduction was more pronounced in 12-month-old animals.

Furthermore, the mitochondrial membrane potential, an index for the integrity of mitochondrial function, was reduced in cortical cells from ^{triple}AD mice at 8 months and from APP–PS2 mice at 12 months. The decrease in complex I and IV activity and mitochondrial membrane potential at 12 months was accompanied by a drop in ATP levels and an increase in levels of superoxide anion and cytosolic reactive oxygen species in cortical neurons, but not in cerebellar neurons, indicating a region-specific dysfunction of cellular energy homeostasis.

These results suggest that the effects of pathological Aβ and tau aggregates converge synergistically on mitochondria in a region-specific manner. These studies may lead to the exploitation of mitochondrial targets for the development of treatments for AD.

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ORIGINAL RESEARCH PAPER Rhein, V. *et al.* Amyloid-β and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. *Proc. Natl Acad. Sci. USA* 6 Nov 2009 (doi:10.1073/pnas.0905529106)

FURTHER READING Bayés, A. & Grant, S. G. N. Neuroproteomics: understanding the molecular organization and complexity of the brain. *Nature Rev. Neurosci.* **10**, 635–646 (2009)