Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis

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Increasing evidence suggests an important role of mitochondrial dysfunction in the pathogenesis of Alzheimer's disease. Thus, we investigated the effects of acute and chronic exposure to increasing concentrations of amyloid beta (Abeta) on mitochondrial function and nitric oxide (NO) production in vitro and in vivo. Our data demonstrate that PC12 cells and human embryonic kidney cells bearing the Swedish double mutation in the amyloid precursor protein gene (APPsw), exhibiting substantial Abeta levels, have increased NO levels and reduced ATP levels. The inhibition of intracellular Abeta production by a functional gamma-secretase inhibitor normalizes NO and ATP levels, indicating a direct involvement of Abeta in these processes. Extracellular treatment of PC12 cells with comparable Abeta concentrations only leads to weak changes, demonstrating the important role of intracellular Abeta. In 3-month-old APP transgenic (tg) mice, which exhibit no plaques but already detectable Abeta levels in the brain, reduced ATP levels can also be observed showing the in vivo relevance of our findings. Moreover, we could demonstrate that APP is present in the mitochondria of APPsw PC12 cells. This presence might be directly involved in the impairment of cytochrome c oxidase activity and depletion of ATP levels in APPsw PC12 cells. In addition, APPsw human embryonic kidney cells, which produce 20-fold increased Abeta levels compared with APPsw PC12 cells, and APP tg mice already show a significantly decreased mitochondrial membrane potential under basal conditions. We suggest a hypothetical sequence of pathogenic steps linking mutant APP expression and amyloid production with enhanced NO production and mitochondrial dysfunction finally leading to cell death.

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