Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 107138
Author(s) Rhein, Virginie; Song, Xiaomin; Wiesner, Andreas; Ittner, Lars M; Baysang, Ginette; Meier, Fides; Ozmen, Laurence; Bluethmann, Horst; Dröse, Stefan; Brandt, Ulrich; Savaskan, Egemen; Czech, Christian; Götz, Jürgen; Eckert, Anne
Author(s) at UniBasel Eckert, Anne ;
Year 2009
Title Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice
Journal Proceedings of the National Academy of Sciences of the United States of America
Volume 106
Number 47
Pages / **Article-Number** 20057-62
Keywords amyloid-beta peptide, electron transport chain, energy metabolism, mitochondrial complexes, tau protein
Alzheimer's disease (AD) is characterized by amyloid-beta (Abeta)-containing plaques, neurofibrillary tangles, and neuron and synapse loss. Tangle formation has been reproduced in P301L tau transgenic pR5 mice, whereas APP(sw)PS2(N141I) double-transgenic APP152 mice develop Abeta plaques. Cross-breeding generates triple transgenic ((triple)AD) mice that combine both pathologies in one model. To determine functional consequences of the combined Abeta and tau pathologies, we performed a proteomic analysis followed by functional validation. Specifically, we obtained vesicular preparations from (triple)AD mice, the parental strains, and nontransgenic mice, followed by the quantitative mass-tag labeling proteomic technique iTRAQ and mass spectrometry. Within 1,275 quantified proteins, we found a massive deregulation of 24 proteins, of which one-third were mitochondrial proteins mainly related to complexes I and IV of the oxidative phosphorylation system (OXPHOS). Notably, deregulation of complex I was tau dependent, whereas deregulation of complex IV was Abeta dependent, both at the protein and activity levels. Synergistic effects of Abeta and tau were evident in 8-month-old (triple)AD mice as only they showed a reduction of the mitochondrial membrane potential at this early age. At the age of 12 months, the strongest defects on OXPHOS, synthesis of ATP, and reactive oxygen species were exhibited in the (triple)AD mice, again emphasizing synergistic, age-associated effects of Abeta and tau in perishing mitochondria. Our study establishes a molecular link between Abeta and tau protein in AD pathology in vivo, illustrating the potential of quantitative proteomics.

Publisher National Academy of Sciences
ISSN/ISBN 0027-8424
edoc-URL http://edoc.unibas.ch/dok/A5253433
Full Text on edoc No;
Digital Object Identifier DOI 10.1073/pnas.0905529106
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/19897719
ISI-Number WOS:000272180900058
Document type (ISI) Journal Article