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Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease

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Abstract

Mitochondrial dysfunction has been proposed to play a pivotal role in neurodegenerative diseases, including Alzheimer's disease (AD). To address whether mitochondrial dysfunction precedes the development of AD pathology, we conducted mitochondrial functional analyses in female triple transgenic Alzheimer's mice (3xTg-AD) and age-matched nontransgenic (nonTg). Mitochondrial dysfunction in the 3xTg-AD brain was evidenced by decreased mitochondrial respiration and decreased pyruvate dehydrogenase (PDH) protein level and activity as early as 3 months of age. 3xTg-AD mice also exhibited increased oxidative stress as manifested by increased hydrogen peroxide production and lipid peroxidation. Mitochondrial amyloid beta (Abeta) level in the 3xTg-AD mice was significantly increased at 9 months and temporally correlated with increased level of Abeta binding to alcohol dehydrogenase (ABAD). Embryonic neurons derived from 3xTg-AD mouse hippocampus exhibited significantly decreased mitochondrial respiration and increased glycolysis. Results of these analyses indicate that compromised mitochondrial function is evident in embryonic hippocampal neurons, continues unabated in females throughout the reproductive period, and is exacerbated during reproductive senescence. In nontransgenic control mice, oxidative stress was coincident with reproductive senescence and accompanied by a significant decline in mitochondrial function. Reproductive senescence in the 3xTg-AD mouse brain markedly exacerbated mitochondrial dysfunction. Collectively, the data indicate significant mitochondrial dysfunction occurs early in AD pathogenesis in a female AD mouse model. Mitochondrial dysfunction provides a plausible mechanistic rationale for the hypometabolism in brain that precedes AD diagnosis and suggests therapeutic targets for prevention of AD.

Figures

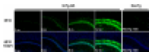

Fig. 1. Age-related increase in Aβ-IR in...

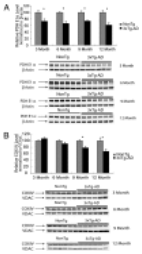

Fig. 2. 3xTg-AD female mice have decreased...

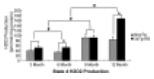

Fig. 3. 3xTg-AD female mice exhibit higher...

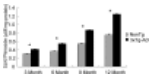

Fig. 4. 3xTg-AD female mice exhibit higher...

Fig. 5. 3xTg-AD female mice exhibit decreased...

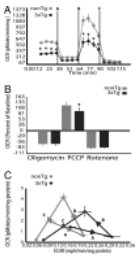

Fig. 6. Hippocampal neurons derived from 3xTg-AD...

All figures (7)

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