Annals of General Psychiatry

BioMed Central

Poster presentation

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Neuropathology and reduced CREB/CBP signaling in presenilin conditional knockout mice: Prospects for therapy of Alzheimer's disease

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from International Society on Brain and Behaviour: 2nd International Congress on Brain and Behaviour
Thessaloniki, Greece. 17–20 November 2005

Published: 28 February 2006

Annals of General Psychiatry 2006, **5**(Suppl 1):S233 doi:10.1186/1744-859X-5-S1-S233

Background

Mutations in presenilins (PS1 and PS2) are the major cause of familial Alzheimer's disease (FAD). FAD-linked PS mutations are generally thought to lead to AD pathogenesis through their property to increase the levels of the toxic peptide beta-amyloid 42 (Abeta42). Although a large body of information exists on the biochemistry and cell biology of presenilins, the normal function of presenilins in the adult mammalian brain has been largely unknown.

Materials and methods

To overecome the embryonic lethality of PS1/PS2-null mice, we used the Cre-loxP system to generate PS conditional double knockout (PS cDKO) mice lacking both presenilins in the postnatal forebrain. Brain morphology and inflammatory responses in these mice were examined by histological methods. Investigation of the molecular events underlying the phenotypes of PS cDKO mice was performed by quantitative real-time RT-PCR, Western blot and oligonucleotide microarrays.

Results

PS cDKO mice exhibit impairments of hippocampal memory and synaptic plasticity which manifest at a young age (data not shown). These deficits are followed by age-dependent neurodegeneration and enlargement of the lateral ventricles. Microarray analysis revealed alterations in the expression of a high number of genes, most notably up-regulation of a group of inflammatory genes. Strong astrocytic and microglial activations and high levels of the inflammatory proteins complement component C1q and cathepsin S were identified in the brain of PS cDKO mice. Examination of the CREB/CBP signaling pathway, which is important for memory formation and neuronal survival, showed reduced expression of multiple CREB/CBP target genes in PS cDKO mice, likely mediated through transcriptional regulation of CBP by Notch signaling, which is known to be controlled by presenilins.

Discussion

The presence of phenotypes in PS cDKO mice that resemble major characteristics of AD, such as progressive memory decline and neuronal degeneration, suggest that FAD-linked PS mutations lead to the pathogenesis of the disease through a partial loss-of-function mechanism, in concert with the proposed gain-of-function mechanism that is responsible for increased production of Abeta42. The identification that CREB/CBP signaling is regulated by presenilins, together with previous results showing that Abeta42 inhibits CREB activation (1, 2) suggest that pharmacological enhancement of CREB/CBP activity could be an effective means for therapy of AD.

References

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