Pathobiological Studies of BACE1 and APP in Alzheimers Diseases

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Principal Investigators

CAI, HUAIBIN

Institution

National Institute on Aging

Contact information of lead PI
Country

USA

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Research Abstract

1. BACE1 elevation is involved in amyloid plaque development in the triple transgenic model of Alzheimers disease: Differential A-beta antibody labeling of early-onset axon terminal pathology. APP and presenilins mutations cause early-onset familial Alzheimers disease (FAD). Some FAD-based mouse models produce amyloid plaques, others dont. Beta-Amyloid (A-beta) deposition can manifest as compact and diffuse plaques; it is unclear why the same A-beta molecules aggregate in different patterns. Is there a basic cellular process governing A-beta plaque pathogenesis? We showed in some FAD mouse models that compact plaque formation

is associated with a progressive axonal pathology inherent with increased expression of beta-secretase (BACE1), the enzyme initiating the amyloidogenic processing of APP. A monoclonal A antibody, 3D6, visualized distinct axon terminal labeling before plaque onset. The present study was set to understand BACE1 and axonal changes relative to diffuse plaque development and to further characterize the novel axonal A antibody immunoreactivity (IR), using triple transgenic AD (3xTg-AD) mice as experimental model. Diffuse-like plaques existed in the forebrain in aged transgenics and were regionally associated with increased BACE1 labeled swollen/sprouting axon terminals. Increased BACE1/3D6 IR at axon terminals occurred in young animals before plaque onset. These axonal elements were also co-labeled by other antibodies targeting the N-terminal and mid-region of A-beta domain and the C-terminal of APP, but not co-labeled by antibodies against the A-beta C-terminal and APP N-terminal. The results suggest that amyloidogenic axonal pathology precedes diffuse plaque formation in the 3xTg-AD mice, and that the early-onset axonal A-beta antibody IR in transgenic models of AD might relate to a cross-reactivity of putative APP beta-carboxyl terminal fragments. 2. In vivo Olfactory Model of APP-induced Neurodegeneration Reveals a Reversible Cell-autonomous Function. APP has long been linked to the neurodegeneration of Alzheimers disease (AD), but the associated cell death has been difficult to capture in vivo, and the role of APP in effecting neuron loss is still unclear. Olfactory dysfunction is an early symptom of AD with amyloid pathology in the olfactory epithelium correlating well to the brain pathology of AD patients. As olfactory sensory neurons (OSNs) regenerate continuously with immature and mature OSNs co-existing in the same olfactory epithelium, we sought to utilize this unique system to study APP-induced neurodegeneration. Here we have developed an olfactory-based transgenic mouse model that overexpresses humanized-APP containing familial AD-mutations (hAPP) in either mature or immature OSNs, and found that despite the absence of extracellular plaques a striking number of apoptotic neurons were detected by 3 weeks of age. Importantly, apoptosis was restricted to the specific population overexpressing hAPP, either mature or immature OSNs, sparing those without hAPP. Interestingly, we observed that this widespread neurodegeneration could be rapidly rescued by reducing hAPP expression levels in immature neurons. Together, these data argue that overexpressing hAPP alone could induce cell autonomous apoptosis in both mature and immature neurons, challenging the notion that amyloid plaques are necessary for neurodegeneration. Furthermore, we show that hAPP induced neurodegeneration is reversible, suggesting that AD-related neural loss could potentially be rescued. Thus, we propose that this unique in vivo model will not only help determine the mechanisms underlying AD-related neurodegeneration but also serve as a platform to test possible treatments.

Further information available at:

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