TAU-DEPENDENT MICROTUBULE DISASSEMBLY INDUCED BY PRE-FIBRILLAR BETA-AMYLOID: A SEMINAL CELL BIOLOGICAL EVENT IN ALZHEIMER'S DISEASE?

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Alzheimer's Disease (AD) is defined histopathologically by extracellular ß-amyloid (Aß) fibrils plus intraneuronal tau filaments. Studies of transgenic mice and cultured cells indicate that AD is caused by a pathological cascade in which Aß lies upstream of tau, but the steps that connect Aß to tau have remained undefined. Here we demonstrate that tau confers acute, reversible hypersensitivity of microtubules to pre-fibrillar, extracellular Aß in non-neuronal cells that express transfected tau and in cultured neurons that express endogenous tau. Pre-fibrillar Aß42 was active at submicromolar concentrations, several-fold below those required for equivalent effects of pre-fibrillar Aß40, and microtubules were insensitive to fibrillar Aß. The active region of tau was localized to an N-terminal domain that does not bind microtubules and is not part of the region of tau that assembles into filaments. These results suggest that a seminal cell biological event in AD pathogenesis is acute, tau-dependent loss of microtubule integrity caused by exposure of neurons to readily diffusible Aß.

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