Cellular And Molecular Pathogenesis Of Alzheimer

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Research Abstract

Approximately 5 million Americans currently suffer from Alzheimers disease (AD) a neurodegenerative disorder characterized by progressive impairment of cognitive function and emotional and sleep disturbances. This laboratory has developed cell culture and mouse models of AD, and have used these models to elucidate the biochemical and molecular events responsible for neuronal dysfunction and death in AD. Our findings suggest that during aging neurons become increasingly prone to dysfunction as a result of impaired cellular energy

metabolism and destabilization of calcium-regulating systems. Amyloid beta-peptide can exacerbate these age-related changes in neurons resulting in their degeneration and consequent cognitive deficits. Membrane lipid peroxidation appears to play an important role in amyloidogenic processing of the amyloid precursor protein as the lipid peroxidation product 4-hydroxynonenal covalently modifies the protein nicastrin and thereby increases gamma-secretase activity. We have also found that redox enzymes in the plasma membrane play important roles in protecting neurons against membrane lipid peroxidation and Abeta toxicity. The latter findings reveal previously unknown molecular targets for the development of novel therapeutic interventions in AD. We have found that dietary restriction can reduce amyloid deposition and protect neurons from being damaged and killed in animal models of AD, and that this beneficial effect of dietary restriction involves stimulation of the production of brain-derived neurotrophic factor (BDNF). Antidepressant serotonin reuptake inhibitors can reduce amyloid deposition and improve cognitive function in a mouse model of AD, suggesting a potential prophylactic/therapeutic use of such drugs. In addition, we found that a drug called diazoxide, previously used to treat hypertension,reduces amyloid and tau pathologies and improves cognitive function in our 3xTgAD mouse model of AD. In addition, dietary supplementation with nicotinamide retards the disease process in a mouse model of AD by a mechanism involving sustenance of neuronal energy levels and enhanced clearance of abnormal forms of amyloid and tau. We have shown that diabetes causes a deficit in cognitive function which is associated with impaired hippocampal synaptic plasticity and neurogenesis; exercise and dietary energy restriction can counteract these adverse effects of diabetes. Our recent findings suggest that an excitatory imbalance, resulting from reduced GABAergic inhibition, is an early and pivotal event in AD pathogenesis. We recently demonstrated a therapeutic benefit of drugs used to improve glycemic control in animal models of diabetes and Alzheimer’s disease, and we have initiated a clinical trial of one of these drugs, Exenatide, in human subjects with mild cognitive impairment or early stage Alzheimer’s disease. Impaired brain energy metabolism and oxidative stress are implicated in cognitive decline and the pathologic accumulations of amyloid -peptide (A) and hyperphosphorylated tau in vulnerable brain regions. The 3xTgAD mouse model was used to test the hypothesis that a ketone ester-based diet can ameliorate AD pathogenesis. Beginning at a presymptomatic age, 2 groups of male 3xTgAD mice were fed a diet containing a physiological enantiomeric precursor of ketone bodies (KET) or an isocaloric carbohydrate diet. The results of behavioral tests performed at 4 and 7 months after diet initiation revealed that KET-fed mice exhibited significantly less anxiety in 2 different tests. 3xTgAD mice on the KET diet also exhibited significant, albeit relatively subtle, improvements in performance on learning and memory tests. Immunohistochemical analyses revealed that KET-fed mice exhibited decreased Abeta; deposition in the subiculum, CA1 and CA3 regions of the hippocampus, and the amygdala. KET-fed mice exhibited reduced levels of hyperphosphorylated tau deposition in the same regions of the hippocampus, amygdala, and cortex. Thus, a novel ketone ester can ameliorate proteopathic and behavioral deficits in a mouse AD model. We explored the role of DNA damage processing in the progression of cognitive decline by creating a new mouse model. The new model is a cross of a common Alzheimer’s disease (AD) mouse (3xTgAD), with a mouse that is heterozygous for the critical DNA base excision repair enzyme, DNA polymerase . A reduction of this enzyme causes neurodegeneration and aggravates the AD features of the 3xTgAD mouse, inducing neuronal dysfunction, cell death and impairing memory and synaptic plasticity. Transcriptional profiling revealed remarkable similarities in gene expression alterations in brain tissue of human AD patients and 3xTg/Pol(+/-) mice including abnormalities suggestive of impaired cellular bioenergetics. Our findings demonstrate that a

modest decrement in base excision repair capacity can render the brain more vulnerable to AD-related molecular and cellular alterations. AD patients typically exhibit impaired olfaction associated with neuronal degeneration in the olfactory bulb (OB). Because DNA base excision repair (BER) is reduced in brain cells during normal aging and AD, we determined whether inefficient BER due to reduced DNA polymerase- (Pol) levels renders OB neurons vulnerable to degeneration in the 3xTgAD mouse model of AD. We interrogated OB histopathology and olfactory function in wild type and 3xTgAD mice with normal or reduced Pol levels. Compared to wild type control mice, Pol heterozygous (Pol+/-) and 3xTgAD mice, 3xTgAD/Pol+/- mice exhibited impaired performance in a buried food test of olfaction. Pol deficiency did not affect the proliferation of OB neural progenitor cells in the subventricular zone. However, numbers of newly generated neurons were reduced by approximately 25% in Pol+/- and 3xTgAD mice, and by over 60% in the 3xTgAD/Pol+/- mice compared to wild type control mice. Analyses of DNA damage and apoptosis revealed significantly greater degeneration of OB neurons in 3xTgAD/Pol+/- mice compared to 3xTgAD mice. Levels of amyloid -peptide (A) accumulation in the OB were similar in 3xTgAD and 3xTgAD/Pol+/- mice, and cultured Pol-deficient neurons exhibited increased vulnerability to A-induced death. Olfactory deficit is an early sign in human AD, but the mechanism is not yet understood. Our findings in a new AD mouse model demonstrate that diminution of BER can endanger OB neurons, and suggest a mechanism underlying early olfactory impairment in AD.

Further information available at:

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