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Alzheimers Congress 2019: Stress-induced Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disease that is both progressive and fatal. Clinical trials focused on pathogenic hypotheses of extracellular/intracellular protein aggregation caused by oxidative stress or other environmental insults have had setbacks recently. We present a major and serendipitous case of an AD patient in this paper. It's the first time a single patient has been followed for more than 32 years, where the signs of Alzheimer's disease have shown up and gone away many times. In the five episodes of extreme stress, the symptoms of stress resulting in a variety of illnesses, such as memory loss, brain atrophy, high blood pressure, inflammations, decreased immunity, and so on, were found, suggesting that the disease is stress-induced. Seven everyday anti-stress strategies were introduced as part of an anti-stress lifestyle. We discovered a connection between stress/stress hormones and strain/stress hormone impact, as well as the pathways leading to a stress-induced molecular mechanism that explains toxic free radicals (oxidants) and A? and Tau (anti-oxidants). Our mechanism may be extended to other neurodegenerative disorders involving protein stress responses, such as Parkinson's disease and alpha-syncline.

Alzheimer's disease is caused by the gradual accumulation of amyloid-peptide (Aβ) and subsequent degeneration of neurons in brain regions involved in learning and memory due to changes in the brain that occur as people age. Two factors that are believed to contribute to neuronal dysfunction and degeneration in AD are increased oxidative stress and increased production of neurotoxic styles of Aβ. Alterations in lipid metabolism might also play roles in AD because the danger of AD is suffering from inheritance of various isoforms of apolipoprotein E, changes in cholesterol metabolism can affect Aβ production in cell culture and in vivo, and medicines that lower cholesterol levels may reduce the danger of AD. However, an immediate link between alterations within the metabolism of cholesterol and other membrane lipids in AD has not been established, and it's not known whether and the way such lipid alterations might result in neuronal dysfunction and death.

Membrane microdomains that are rich in cholesterol and sphingolipids play important roles in various cellular signaling pathways. Sphingomyelin may be a major source of ceramides, lipid mediators that are generated when sphingomyelin is cleaved by sphingomyelinases, enzymes activated by inflammatory cytokine, and oxidative stress. Ceramides play important roles in regulating an array of physiological processes, including cell proliferation and differentiation, and a sort of programmed death called apoptosis. In the present study, we document significant increases in levels of membrane-associated oxidative stress, long-chain ceramides, and free cholesterol in brain cells during normal aging in mice, in AD patients, and in neurons exposed to Aβ. The intracellular accumulation of ceramides and cholesterol, and therefore the neurotoxicity of Aβ, will be blocked by α-tocopherol and a small-molecule inhibitor of ceramide production, suggesting a possible therapeutic good thing about agents that focus on sphingolipid metabolism in AD.

The present findings document abnormalities in sphingolipid and cholesterol metabolism within the brain during normal aging, and within the brains of AD patients compared with age-matched controls. Data from studies during which neurons were exposed to Aβ suggest that this neurotoxic peptide could also be liable for the membrane lipid abnormalities in AD, which the lipid alterations could also be a pivotal event within the neurotoxic effects of Aβ. When taken along with previous findings documenting increased oxidative stress in brain aging and AD, these findings suggest the subsequent sequence of events within the pathogenesis of AD. Genetic and/or environmental factors, along with the aging process, end in altered proteolytic processing of the amyloid precursor protein and increased Aβ production and aggregation. Aβ induces membrane-associated oxidative stress, which alters membrane lipid metabolism, leading to increased amounts of ceramides and cholesterols. The derangements of sphingolipid and cholesterol metabolism, together with oxidative stress, cause synaptic dysfunction and neuronal degeneration. The perturbed cholesterol and sphingolipid metabolism may, in turn, enhance the assembly of Aβ1–42 by facilitating γ-secretase cleavage of amyloid precursor protein, as suggested by recent studies.

Our data suggest that perturbed membrane lipid metabolism in AD may result, a minimum of partially, from increased Aβ production/deposition, which the increased ceramide production resulting from the oxidative stress induced by Aβ may trigger the death of neurons. We found that levels of HNE were significantly increased in brain tissues of AD patients, which is in line with previous data suggesting that oxidative stress is an early and pivotal event within the neurodegenerative process in AD. Oxidative stress induced by Aβ1–42 and HNE caused ceramide accumulation in hippocampal neurons, which is in step with previous studies showing that oxidative stress increases and antioxidants decrease ceramide levels in tumor cells. ISP-1 prevented Aβ-induced death of hippocampal neurons, suggesting pivotal roles for sphingomyelin metabolism and ceramide production in amyloid neurotoxicity. When sphingomyelin levels were reduced by treatment of cells with ISP-1, the assembly of ceramides in response to Aβ was decreased, which was in keeping with sphingomyelin being the source of the ceramides. Ceramides may trigger apoptosis in both physiological and pathological settings. as an example, it's been shown that ceramide analogs can induce caspase-3 activation and poly (ADP-ribose) polymerase cleavage, and overexpression of the antiapoptotic protein Bcl-2 can prevent ceramide-induced apoptosis. the current findings, therefore, suggest a job for excessive ceramide production in neuronal death in AD.

Increasing evidence supports the involvement of perturbed cholesterol metabolism within the pathogenesis of AD. Individuals with an apolipoprotein E4 allele are at increased risk of AD, and epidemiological data suggest that individuals prescribed cholesterol-lowering drugs are at reduced risk of AD. Oxidative stress could also be a crucial factor that promotes the types of derangements of cholesterol and sphingolipid metabolism that occur in AD. Studies of non-neuronal cells have shown that oxidative stress and ceramide production can increase the buildup of cholesterol in cells.

High levels of free cholesterol can be toxic to cells as demonstrated by

the ability of inhibitors of ACAT to induce apoptosis and by the ability of statins to protect neurons against ischemic/oxidative injury.

Foot Note: This work is partly presented at Joint Event on 11th World Congress on Alzheimer's Disease & Dementia March 20-21, 2019 | Svdnev. Australia