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Commentary

Risk Factors and Mechanisms of Alzheimer's Disease Pathogenesis: Obviously and Obviously Not

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In their article, Chen and Fernandez (3) present a viewpoint in which they briefly consider the roles of the aging process, and risk factors associated with age-related degenerative diseases, in the pathogenesis of Alzheimer's disease (AD). The authors forward both the general perspective, and a specific mechanism which they suggest underlies most cases of AD. They propose that 1) "several known risk factors most likely play a critical role in the late-onset sporadic AD", and 2) "plaques and tangles occur spontaneously during aging as a result of a natural decline of energy metabolism and Ca^{2+} signaling." My responses to these two major conclusions are that 1) obviously, genetic and environmental risk factors play important roles in the pathogenesis of AD, and this is certainly not a new perspective; and 2) the proposal that a decline in energy metabolism and Ca^{2+} signaling is central to the pathogenesis of AD is obviously not correct. In the following paragraphs I will elaborate on these two points.

It is obviously the case that there are several important risk factors that increase the probability of developing AD. The aging process is the strongest risk factor for AD, and the molecular and cellular changes that occur in the brain during aging are therefore germane to the pathogenesis of AD. However, there are clearly additional genetic and environmental risk factors that impact on events occurring at the molecular, biochemical and cellular levels in AD. Several excellent examples of risk factors were presented nicely by Chen and Fernandez. Genetic risk factors include apolipoprotein E allele variations with the E4 allele increasing risks for AD (25). The mechanism whereby apolipoprotein E isoforms modify vulnerability of neurons during aging and in AD appears to involve an antioxidant-like property of apolipoprotein E (20) with apolipoprotein E2 being very effective in binding to and detoxifying the neurotoxic product of membrane lipid peroxidation, 4-hydroxy-nonenal (22). A deletion at the 5' splice site of exon II of α2 macroglobulin also increases risk for AD (1), although the precise mechanism remains to be determined. Environmental risk factors having to do with diet and behavior are becoming clearer. One of the major risk factors for AD that is emerging from recent work is high calorie intake or overeating, a known risk factor for other age-related diseases including cardiovascular disease, diabetes and cancer. Recent epidemiological data suggest that individuals with a low calorie intake are at reduced risk for AD and Parkinson's disease (8,15,19). Experimental data also support the possibility that reducing calorie intake will reduce risks for, and severity of, several age-related neurodegenerative disorders including AD. Administration of the excitotoxin kainate to adult rats results in selective damage to hippocampal neurons and impaired learning and memory. Maintenance of rats on a dietary restriction regiment results in increased resistance of hippo-

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campal neurons to kainate-induced damage and amelioration of deficits in learning and memory (2). In addition, maintenance of presenilin1 mutant knockin mice on a dietary restriction regimen results in reduced levels of oxidative stress and reduced neuronal damage following kainate administration (27). Similar beneficial effects of dietary restriction have been reported in experimental animal models of Parkinson's disease, Huntington's disease and stroke (2,5,26). Data in the latter studies suggest that the beneficial effect of dietary restriction involves a "pre-conditioning response" in which levels of stress proteins and neurotrophic factors are increased. The latter mechanism is of considerable interest when considering the mechanism whereby increased education reduces risk for AD (13). When taken together with animal studies in which rodents are raised in an "intellectually enriched environment (6), the available data suggest that using your brain increases its resistance to age-related neurodegenerative disorders such as AD.

It is now very clear, based on considerable data from analyses of AD patients and experimental models of AD, that many of the fundamental cellular and molecular events that occur in the brain in this disorder are also manifest in organ systems other than the brain. For example, it is very clear that alterations in energy metabolism occur in AD patients and apparently precede the neurodegenerative process. Brain imaging studies clearly reveal decreased glucose uptake into neurons in the brains of AD patients (12), and APP mutant transgenic mice exhibit reduced glucose uptake that becomes evident in the early stages of amyloid deposition (4). This alteration may result from oxidative impairment of glucose transporters caused by amyloid β-peptide deposition in conjunction with age-related increases in oxidative stress (16). In addition, studies of peripheral cells, such as fibroblasts, from AD patients suggest that deficits in energy metabolism are not limited to the brain (7). Moreover, recent studies of APP mutant transgenic mice demonstrate profound alterations in stress responses and energy metabolism (23). The latter study showed that APP mutant transgenic mice exhibit altered regulation in blood glucose levels following several different stresses, including restraint stress and food deprivation, such that the animals become severely hypoglycemic. A second example of widespread alterations in AD concerns functions of the immune system. Many studies have documented alterations in lymphocyte signaling and function in AD patients (11). Our recent studies of presenilin 1 mutant mice and APP mutant mice suggest related alterations occur in the immune system of these mouse models of AD (manuscript in preparation).

The author's contention (3) that plaques and tangles arise from a deficit in Ca^{2+} signaling is, in my view, not only unfounded, but exactly opposite of what available data suggest. Many different laboratories have provided evidence obtained from analyses of AD patients and experimental animal and cell culture models, that there is an increase in intracellular Ca^{2+} levels in neurons that occurs during aging and in AD, and that the increase in intracellular Ca^{2+} levels contributes to the demise of the neurons. For example, Landfield and colleagues (1) have shown that calcium influx increases in hippocampal neurons during aging in rodent, and Nixon and coworkers (21) have clearly shown that activation of Ca^{2+}-dependent proteases increases in degenerating neurons in AD. We have shown that increases in intracellular Ca^{2+} levels can elicit changes in the cytoskeleton of neurons similar to those seen in neurofibrillary tangles (17,24), and that amyloid β-peptide disrupts Ca^{2+} regulation in a manner that increases Ca^{2+} influx and increases vulnerability of neurons to various insults relevant to AD including excitotoxicity and apoptosis (18). Moreover, a primary effect of presenilin-1 mutations is to disturb Ca^{2+} regulation in the endoplasmic reticulum which results in enhanced levels of intracellular Ca^{2+} following exposure of neurons to oxidative, metabolic and excitotoxic insults (9,10). The author's (3) contention that Ca^{2+} signaling potency is reduced during aging is directly against an overwhelming body of evidence showing that age-related changes known to occur in the brain, including increased oxidative stress and decreased energy availability, promote increases in intracellular Ca^{2+} levels rather than decreases. Thus, oxidative stress impairs the

function of ion-motive ATPases and other Ca^{2+}-regulating proteins which promote membrane depolarization and Ca^{2+} influx. Similarly, reduced glucose availability to neurons results in reduced ATP levels and reduced ability of neurons to remove Ca^{2+} via energy dependent pumps. Finally, the known risk factors for AD would also tend to promote elevations in intracellular Ca^{2+} levels. For example, head trauma and cerebral ischemia both increase intracellular Ca^{2+} levels in neurons which contributes to their degeneration under these adverse conditions. Moreover, the emerging mechanism for the beneficial effects of dietary restriction, and activity in neuronal circuits, involves stabilization of intracellular calcium levels as the result of enhanced neurotrophic factor signaling and stress protein production (5,26).

In conclusion, the article by Chen and Fernandez (3) provides a useful, albeit obvious, view of the importance risk factors for AD pathogenesis. On the other hand, the authors appear to be quite off the mark concerning the roles of dysregulation of Ca^{2+} homeostasis and energy metabolism in the pathogenesis of AD.

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