Existing Data Suggest That Alzheimer's Disease Is Preventable

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ABSTRACT: The ultimate goal of Alzheimer's disease (AD) research is to prevent the onset of the neurodegenerative process and thereby allow successful aging without cognitive decline. Herein I argue that a simple and effective preventative approach for AD may be in hand. AD is a disorder associated with the aging process and is, accordingly, characterized by cellular and molecular changes that occur in age-related diseases in other organ systems. Such changes include increased levels of oxidative stress, perturbed energy metabolism, and accumulation of insoluble (oxidatively modified) proteins (prominent among which are amyloid β-peptide and tau). The risk of several other prominent age-related disorders, including cardiovascular disease, cancer, and diabetes, is known to be influenced by the level of food intake—high food intake increases risk, and low food intake reduces risk. An overwhelming body of data from studies of rodents and monkeys has documented the profound beneficial effects of dietary restriction (DR) in extending life span and reducing the incidence of age-related diseases. Reduced levels of cellular oxidative stress and enhancement of energy homeostasis contribute to the beneficial effects of DR. Recent findings suggest that DR may enhance resistance of neurons in the brain to metabolic, excitotoxic, and oxidative insults relevant to the pathogenesis of AD and other neurodegenerative disorders. While further studies will be required to establish the extent to which DR will reduce the incidence of AD, it would seem prudent (based on existing data) to recommend DR as widely applicable preventative approach for age-related disorders including neurodegenerative disorders.

KEYWORDS: Amyloid; Apoptosis; Calorie restriction; Diet; Glucose; Neurotrophic factor

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CELLULAR AND MOLECULAR UNDERPINNINGS OF THE NEURODEGENERATIVE PROCESS IN AD

Studies of Alzheimer's disease (AD) patients have provided quite convincing evidence that the neurodegenerative process is associated with increased levels of cellular oxidative stress.[1] In addition, metabolic abnormalities, typified by reduced glucose availability to brain cells and widespread alterations in mitochondrial function, occur in AD.[2] The causes of these alterations are likely to include fundamental age-related changes, in combination with perturbed APP metabolism. Aβ clearly plays an important role in promoting synaptic degeneration and neuronal cell death in AD. In addition to the fact that many degenerating neurons are associated with fibrillary Aβ deposits in AD brain, experimental data show that Aβ can induce oxidative stress (membrane lipid peroxidation) in neurons. Such oxidative stress impairs the function of several vital membrane transporters, including ion-motive ATPases (sodium and calcium pumps), glucose transporters, and glutamate transporters. This leads to disruption of cellular calcium homeostasis and mitochondrial dysfunction and thereby renders neurons vulnerable to apoptosis and excitotoxicity.[3] Biochemical cascades implicated in the neurodegenerative process in AD include those involving Par-4 and caspases; these cascades appear to be initiated in synaptic compartments and then propagate to the cell body.[4,5] In support of this scenario are experimental data showing that antioxidants, calcium-stabilizing agents, Par-4–suppressing agents, and caspase inhibitors protect neurons against Aβ toxicity and other AD-related insults. Moreover, the beneficial effect of estrogen in reducing risk for AD

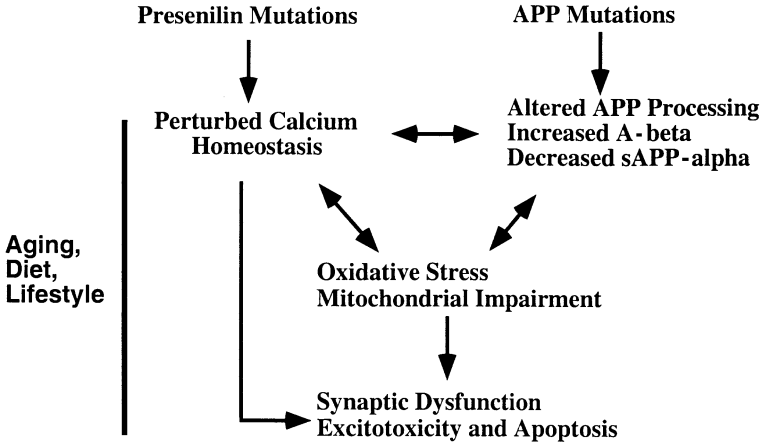

FIGURE 1. General model for the mechanisms whereby genetic and environmental factors may promote neuronal degeneration in AD.

appears to result from an antioxidant activity of this steroid, and vitamin E appears to be effective in slowing the progression of AD.

Studies of the pathogenic actions of genetic mutations that cause early-onset AD provide further compelling support for the neurodegenerative cascade described in the preceding paragraph[3,6] (FIG. 1). APP mutations promote oxidative stress and metabolic compromise by altering APP processing in a manner that increases Aβ (particularly Aβ42) production and reduces levels of sAPPα.[3] As described in the preceding paragraph, Aβ promotes neuronal apoptosis and excitotoxicity. Conversely, sAPPα is a neurotrophic derivative of APP that can protect neurons in culture and *in vivo* against excitotoxic, metabolic, and oxidative injury. Additional data from studies of AD patients suggest that reduced levels of sAPPα contributes to the neurodegenerative process in AD. Studies of transgenic mice expressing AD-linked APP mutations are consistent with the involvement of aberrant APP processing and increased cellular oxidative stress in the pathogenesis of AD. Many cases of early-onset inherited AD result from mutations in presenilins. Studies of cultured cells and transgenic and knockin mice expressing presenilin mutations have shown that the mutations lead to increased neuronal vulnerability to apoptosis and excitotoxicity[7,8] and also increase production of Aβ42 and decrease production of sAPPα.[9] Our data suggest that a major (primary?) alteration in neurons expressing presenilin mutations is a defect in regulation of calcium homeostasis in the endoplasmic reticulum. This perturbed calcium homeostasis endangers neurons subjected to oxidative, excitotoxic, and apoptotic (e.g., trophic factor withdrawal and Aβ) insults.[6–8] Interestingly, studies of fibroblasts from AD patients with APP and presenilin mutations have revealed disturbances in mitochondrial function and oxidative metabolism.[10] Moreover, some data from studies of glucose metabolism suggest that insulin resistance and a "prediabetic state" may presage AD.[2] *Thus, essentially all of the experimental evidence suggests central roles for increased oxidative stress and metabolic disturbances in the pathogenesis of AD.*

IS A MEANS OF FORESTALLING THE NEURODEGENERATIVE CASCADE IN AD IN HAND?

Given such strong evidence for the involvement of oxidative stress and metabolic compromise in the neurodegenerative process in AD, I argue that an obvious means of reducing the incidence of AD is to reduce average daily calorie intake throughout adult life. Despite the convincing evidence that high food intake is a risk factor for age-related disorders such as cardiovascular disease and diabetes, the possibility that high food intake might also increase risk for neurodegenerative disorders has only recently been explored. Here are a few reasons why it might be expected that reduced life-long food

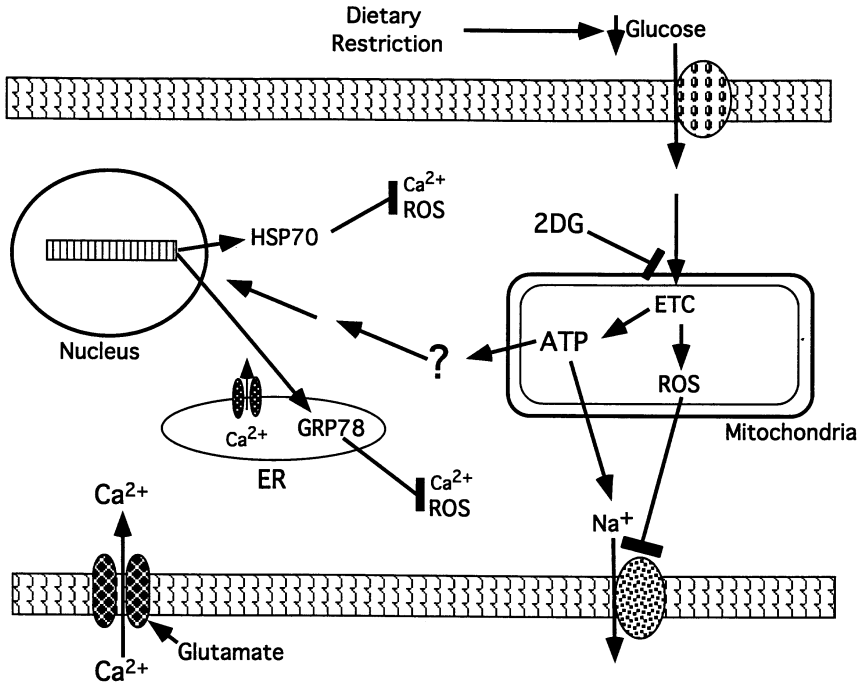

FIGURE 2. Possible mechanisms underlying the neuroprotective effects of dietary restriction. 2DG, 2-deoxy-D-glucose; ER, endoplasmic reticulum; ETC, electron transport chain; GRP78, glucose-regulated protein–78; HSP70, heat-shock protein–70; NTF, neurotrophic factor; ROS, reactive oxygen species.

intake (dietary restriction, DR) will ward off age-related neurodegenerative disorders. including AD. DR dramatically extends the life span and reduces the development of age-related disease in rodents[11] and monkeys.[12] Second, DR reduces levels of oxidative stress in several different organ systems, including the brain.[13] Third, DR attenuates age-related deficits in learning and memory in rodents.[14] Fourth, epidemiological data suggest that the incidences of AD and PD are lower in countries with low per capita food consumption (e.g., China and Japan) compared to countries with high per capita food consumption (e.g., U.S.A. and Canada),[15] and that individuals with a low daily calorie intake are at reduced risk for AD and Parkinson's disease.[16,17]

We have found that DR restriction can protect neurons against degeneration in experimental models of AD and other age-related neurodegenerative disorders. Administration of the excitotoxin kainate to adult rats or mice results in selective damage to the hippocampus and associated deficits in learning and memory. Rats maintained on a DR feeding regimen for 2–4 months exhibit increased resistance of hippocampal neurons to kainate-induced de-

generation, which is correlated with a striking preservation of learning and memory in a water maze spatial learning task.[18] Maintenance of presenilin-1 mutant knockin mice on a DR regimen for 3 months results in increased resistance of hippocampal CA1 and CA3 neurons to kainate-induced injury compared to mice fed ad libitum.[19] Oxidative stress induced by kainate in the hippocampus was decreased in the DR mice compared to mice fed ad libitum, indicating that suppression of oxidative stress may be one mechanism underlying the neuroprotective effect of DR. Thus, the neurodegeneration-promoting effect of a mutation that causes AD can be counteracted by DR. DR also proved beneficial in increasing resistance of neurons to degeneration in experimental models of PD, Huntington's disease, and stroke.[18,20,21] The striking beneficial effects of DR in these experimental models of neurodegenerative disorders, when considered in the light of such epidemiological data, suggest that DR may prove beneficial in reducing the incidence and/or severity of many different human neurodegenerative disorders, including AD.

Calorie restriction may benefit the aging brain in at least two ways. First, by reducing free radical production (as the result of reducing the amount of glucose available to cells), calorie restriction may reduce cumulative damage to proteins, lipids, and DNA. Second, by inducing a mild "stress" in brain cells, calorie restriction may enhance neuronal resistance to apoptosis and excitotoxicity. Our experimental studies showing that DR increases levels of heat-shock protein–70 and glucose-regulated protein–78 in neurons in the brains of rats and mice supports a role for a stress response.[20,21] Moreover, we have found that the beneficial effects of DR in several different animal models of neurodegenerative disorders can be mimicked by administration of 2-deoxy-D-glucose, a nonmetabolizable glucose analogue that restricts energy availability at the cellular level.[20–22]

CONCLUSIONS AND RECOMMENDATIONS

Based upon the data just described and the well-known beneficial effects of reduced calorie intake in preventing atherosclerosis and reducing risk for various cancers, it would seem that sufficient evidence is available to conclude that calorie restriction will be effective in reducing risk for AD and other age-related neurodegenerative disorders. The available data reveal no major surprises and no magic bullets vis-a-vis the neurodegenerative process and therapeutic strategies for AD. As with other major age-related diseases, oxidative stress and metabolic alterations are central to the pathogenesis of AD. Among dietary modifications, reducing calorie intake has the most clear and striking effects in reducing age-related oxidative stress and disease. Increasing intake of antioxidants may have a lesser, but meaningful beneficial effect. It would seem a very safe bet that reducing calorie intake will reduce

risk for AD and other age-related neurodegenerative disorders. Recent and ongoing research strongly support this statement.

It is vital for the future of our aging population that we identify rational and effective approaches that will reduce risk for AD. *Whereas huge sums of money are being spent by pharmaceutical companies (as well as various funding agencies) to support efforts to identify "miracle" drugs to treat symptomatic AD patients, little effort is being placed on identifying and implementing preventative approaches based on diet and lifesyle.* While most would agree that "an ounce of prevention is worth a pound of cure," few in the AD research field are interested in determining whether well-established methods for reducing risk of other age-related diseases will also be effective in forestalling AD.

Integration of the available data described above and expanded upon in the references cited below leads me to propose that *the following measures will reduce risk for AD and other age-related neurodegenerative disorders.*

(1) Limit calorie intake throughout adult life to 1800–2200 calories per day.
(2) Increase intake of antioxidants, such as vitamin E, vitamin C, and the various other antioxidants present in vegetables and fruits.
(3) Increase daily "mental aerobics" (activity in neuronal circuits appears to enhance the resistance of neurons to various insults).
(4) Engage in regular moderate physical excercise, which particularly benefits the vascular system (including cerebral vessels).

This is an approach for preventing AD and is unlikely to halt the neurodegenerative process once it has progressed to the stage where patients are symptomatic (although antioxidant therapy may be of some benefit). Indeed, symptomatic AD patients spontaneously reduce their food intake as the disease progresses.

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