Journal of Alzheimer's Disease 1 (1999) 203–206
IOS Press

Diet and Oxidative Stress: A Novel Synthesis of Epidemiological Data on Alzheimer's Disease*

Mark A. Smith[1,**], Grace J. Petot[2] and George Perry[1]

Departments of Pathology[1] and Nutrition[2], School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA

In an innovative synthesis, William B. Grant links Alzheimer's disease to diet by combining the prevalence of Alzheimer's disease in several countries with a meta-analysis of community-based studies of diet (3). A positive relationship between caloric, as well as fat, intake and the prevalence of Alzheimer's disease is demonstrated. These findings link Alzheimer's disease to diet in a more general sense than previous studies that focused instead on specific dietary components such as consumption of brain, raw meat, seafood, alcohol, coffee or vitamin supplements. These latter studies usually had the single goal of determining whether food-borne pathogens or toxins might be implicated, rather than focusing on foods as a source of nutrients.

Numerous animal studies show prolonged maximum life span and health benefits with caloric restriction (reviewed in (2)), nonetheless, it is perhaps surprising that a multifactorial disease such as Alzheimer's disease appears to be so responsive to total caloric or fat intake ($r \sim 0.9$). While it can be argued that the caloric content of food over many different ethnic groups and individuals simplifies the complex relationship between the many nutrients found in food and the prevalence of Alzheimer's disease, Dr. Grant's analysis points to a clear relationship of diet and Alzheimer's disease and strongly suggests that the initiation and progress of Alzheimer's disease is directly under the control of metabolic balance. Dr. Grant can draw these important conclusions not only because the correlation is high between the food supply and the prevalence of Alzheimer's disease when comparing countries, but also because the incidence changes for ethnic groups when living in, and eating the diet of, different locations. Therefore, when Africans or Japanese live in the United States and adopt a Western diet, their incidence of Alzheimer's disease increases suggesting that it is not the genetics or diagnostic criteria of either Africans or Asians that are responsible for lower incidence but instead a Western lifestyle — including a high caloric diet. Furthermore, ethnic compari-sons also relate to the penetrance of apolipo-protein E e4 allele to increase the incidence of AD (1) since in studies of Africans, apolipo-protein E is not genetically linked to Alzheimer's disease while it is in African-Americans (4). Possibly the distinction lies in the high fat intake of African-Americans compared to Africans which may overwhelm the role of apolipoprotein E in lipid transport and/or affecting the incidence of Alzheimer's disease.

As with most studies of this type, there are a number of potential caveats and the results of analyses of food supply data with prevalence data that are applied to specific populations should be viewed with caution. For example, the dietary data used are from Food Balance Sheets from the FAO and the United States Department of Commerce. These data are based on food production quantities and do not include waste or food

* This article is published with permission from the University of Kentucky. It is also published in the online journal Alzheimer's Disease Review; www.coa.uky.edu/ADReview/

** Corresponding author: M.A. Smith, Institute of Pathology, School of Medicine, Case Western Reserve University, 2085 Adelbert Road, Cleveland, OH 44106, USA, E-mail: mas21@po.cwru.edu

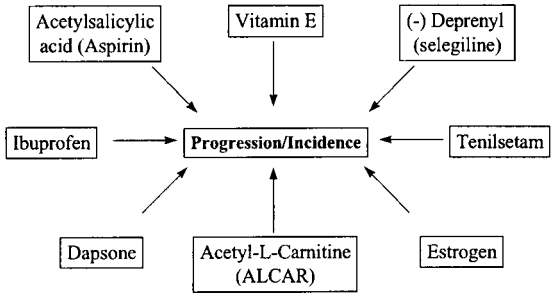

Fig. 1. Factors involved in Alzheimer's disease, centrally impact oxidative stress.

consumed as prepared. Calories and grams of fat from these supply data are calculated, divided by total population and expressed as energy and fat available per capita. In effect, the author is assigning the same calorie and fat values to all individuals regardless of age, personal characteristics, health status, socioeconomic factors, cultural, and regional dietary influences.

The correlations that Dr. Grant makes suggest that total caloric value or low nutrient content, as a consequence of high fat, may be the most significant factor for the onset of Alzheimer's disease. This may provide the important link to the consistent occurrence of Alzheimer's disease as an age-related factor since genetic factors seem to, at most, shift the age of onset. Dr. Grant's thesis not only integrates Alzheimer's disease mechanistically with aging but further suggests that the genetic insights gained from amyloid-β protein, apolipoprotein E and presenilins may be directly related to brain and cellular aging. Dr. Grant suggests that the connection between diet and aging is oxidative stress and given the escalating number of findings, this is an extremely likely postulate (Fig. 1). Indeed, presenilins (10) and β-protein precursor (Kusiak et al., personal communication) are involved in apoptosis, a process of programmed cell death in which oxidative damage plays a prominent role. Furthermore, apolipoprotein E (5) and amyloid-β (Huang et al., personal communication) both bind transition metals, a major requirement for the formation of free radicals.

A case control study of risk factors for Alzheimer's disease is currently in progress at the Alzheimer Center at Case Western Reserve University where we are investigating life style histories of patients and healthy controls. Information requested from subjects includes demographic, medical, occupational, intellectual, educational, smoking and diet histories. A food frequency questionnaire is being used to elicit food patterns for three periods of adult life: ages 20–39 years, ages 40–59 years and ages 60+

Table 1
Dietary patterns throughout life indicate significantly greater consumption by controls than AD cases of Vitamins A C and carotenoids, and more servings per day of foods that contain these nutrients (6). These data strongly support the notion that free radical scavengers, here dietary antioxidants, delay or prevent the onset of Alzheimer's disease.

Nutrients per 1000 kilocalories	AD Cases n = 104	Controls n = 223	p Value
Vitamin A (RE)	855	983	.001
α Carotene (mcg)	294	389	< .001
β Carotene (mcg)	1921	2370	.003
Pro-A Carotene (mcg)	2231	2809	.001
Lutein (mcg)	972	1214	.015
Lycopene (mcg)	666	927	< .001
Vitamin C (mg)	74.6	86.7	.007
Vitamin E (α TE)	5.6	5.9	NS
Servings per day			
Yellow, green vegetables	2.0	2.3	.022
Vitamin C fruits, vegetables	2.4	2.6	NS

Table 2
Caloric intake of Alzheimer's disease and control cases during three periods of adult life, ages 20–39, 40–59 and 60+.

Age Period	Mean	Median	S.D.
20's and 30's			
AD (n = 78)	2115	2051	715
Controls (n = 212)	2092	2100	641
40's and 50's			
AD (n = 108)	2152	2089	710
Controls (n = 225)	2076	2125	648
60+			
AD (n = 84)	2148	2076	702
Controls (n = 232)	1704	1658	487

years. All patterns of food and nutrient intake over time are being analyzed. Preliminary results after five years of data collection for 104 subjects with Alzheimer's disease and 223 controls indicate that controls are consuming significantly greater amounts of antioxidant nutrients: α-carotene, β-carotene, lutein, lycopene and Vitamin C; and significantly more servings of fruits and vegetables (see Table 1). These findings suggest that the exclusion of nutrient rich foods as well as the high caloric content may play a significant role in dietary links to Alzheimer's disease. Further, in this questionnaire, we found that individuals with Alzheimer's disease, presymptomatically, consumed over 400 cal/day more than controls (see Table 2). It is particularly intriguing that the increased caloric consumption of cases that will develop AD is only seen after age 60, suggesting an important link between aging and the differential. These results either suggest that individuals eating a high caloric diet exclude nutrients or instead that individuals with Alzheimer's disease have an inefficient metabolism possibly related to mitochondrial uncoupling. This latter possibility would result in the chronic production of free radicals causing cellular and tissue damage. This source is consistent with the finding that many "at-risk" neurons show increased oxidative damage in Alzheimer's disease, irrespective of whether they contain intraneuronal pathology, i.e., neurofibrillary tangles (7–9). Indeed, many of the factors that affect either the incidence or progression of Alzheimer's disease likely act by reducing oxidative damage (Fig. 2). Further implicating neuronal metabolism, oxidative damage is most often restricted to neuronal cell bodies, not senile plaques nor other brain cell types. When seen in light of the diet analysis, our findings suggest that cells with the highest metabolic rate, i.e., neurons, may be particularly susceptible to metabolic insufficiency that leads to increased metabolism for a given amount of work. Further increased oxidative metabolism will increase oxidative damage including damage to mitochondria that will further increase reactive oxygen species.

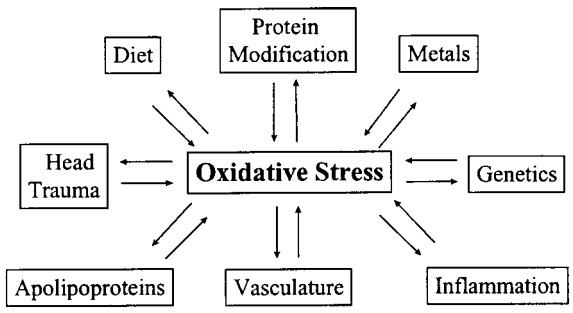

Fig. 2. Therapeutic agents that reduce the progress or incidence of Alzheimer's disease share antioxidant activity.

In summary, the novel link that Dr. Grant has made may open the door to a fundamental understanding of the broad scope of Alzheimer's disease as it relates to metabolism and aging.

Further, this new data adds yet another piece of evidence indicating a prominent role for oxidative stress in disease pathogenesis.

REFERENCES

1. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA, Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families, Science 261 (1993) 921–923.
2. Finch CE, Cohen DM, Aging, metabolism, and Alzheimer disease: review and hypotheses, Exp Neurol 143 (1997) 82–102
3. Grant WB, Dietary links to Alzheimer's disease, Alz Dis Rev 2 (1997) 42–55.
4. Hendrie HC, Osuntokun BO, Hall KS, Ogunniyi AO, Hui SL, Unverzagt FW, Gureje O, Rodenberg CA, Baiyewu O, Musick BS, Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans, Am J Psych 152 (1995) 1485–1492.
5. Miyata M, Smith JD, Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and beta-amyloid peptides, Nature Genetics 14 (1996) 55–61.
6. Petot GJ, Cole R, Conaway C, Debanne SM, Esteban-Santillan C, Koss E, Lerner AJ, Rowland DY, Smyth KA, Whitehouse PJ, Friedland RP, Adult lifetime dietary patterns of antioxidant vitamin and carotenoid consumption in a case control study of risk factors for Alzheimer's disease, 26th Annual Am Aging Assoc Meeting, (1996) 38.
7. Sayre LM, Zelasko DA, Harris PLR, Perry G, Salomon RG, Smith MA, 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease, J Neurochem 68 (1997) 2092–2097.
8. Smith MA, Perry G, Richey PL, Sayre LM, Anderson VE, Beal MF, Kowall N, Oxidative damage in Alzheimer's, Nature 382 (1996) 120–121.
9. Smith MA, Harris PLR, Sayre LM, Beckman JS, Perry G, Widespread peroxynitrite-mediated damage in Alzheimer's disease, J Neurosci 17 (1997) 2653–2657.
10. Wolozin B, Iwasaki K, Vito P, Ganjei JK, Lacana E, Sunderland T, Zhao B, Kusiak JW, Wasco W, D'Adamio L, Participation of presenilin 2 in apoptosis: enhanced basal activity conferred by an Alzheimer mutation, Science 274 (1996) 1710–1713.