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REVIEW ARTICLE

Indices of Metabolic Dysfunction and Oxidative Stress

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Abstract Metabolic alterations are a key player involved in the onset of Alzheimer disease pathophysiology and, in this review, we focus on diet, metabolic rate, and neuronal size differences that have all been shown to play etiological and pathological roles in Alzheimer disease. Specifically, one of the earliest manifestations of brain metabolic depression in these patients is a sustained high caloric intake meaning that general diet is an important factor to take in account. Moreover, atrophy in the vasculature and a reduced glucose transporter activity for the vessels is also a common feature in Alzheimer disease. Finally, the overall size of neurons is larger in cases of Alzheimer disease than that of age-matched controls and, in individuals with Alzheimer disease, neuronal size inversely correlates with disease duration and positively associates with oxidative stress. Overall, clarifying cellular and molecular manifestations involved in metabolic alterations may contribute to a better understanding of early Alzheimer disease pathophysiology.

Keywords Alzheimer disease · Apolipoprotein E · Diet · Metabolism · Neuronal size

Special issue dedicated to John P. Blass.

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Brief introduction

There are a great number of hypotheses concerning Alzheimer disease (AD). The predominant theories focus on specific abnormalities that are used in the diagnosis of disease such as production of amyloid-β ($A\beta_{42}$) [1–3] and τ phosphorylation [4, 5]. As previously discussed [6–8], the lesions of disease should be viewed as surrogates or consequences of the disease process rather than pathogenic. With this in mind, we previously found that oxidative stress precedes both pathologies by decades in both sporadic and familial AD [9–14]. Key factors contributing to oxidative stress in AD are slowly being elucidated with redox metal

ions [15, 16], mitochondria [17], and mitotic alterations being the focus of our groups. Bringing all these aspects together, this review explores the interplay between metabolic factors, which have been implicated in the progression and pathogenesis of AD.

Brain metabolism in Alzheimer disease

John Blass and colleagues presented some of the earliest, and many would say best, biochemical studies of AD highlighting deficiencies in key enzymes of energy metabolism, in particular α-ketoglutarate and pyruvate dehydrogenase [18–20]. Reduced enzymatic activities were not only noted in brain of AD cases but also in other tissues and even in fibroblasts cultured from AD patients. Consistent with this, metabolic imaging studies show reduced glucose utilization as early as, maybe even preceding, the onset of clinical symptoms, in genetically predisposed individuals [21]. Indeed, reduced glucose metabolic rate in the temporoparietal and posterior cingulate cortex is evident in both AD and in subjects with mild cognitive impairment (MCI) [22]. That such metabolic alterations are key contributors to the pathogenesis of AD is highlighted by studies on patients with at least one *ε4* allele of apolipoprotein E (ApoE), where reduced glucose metabolism levels in limbic and associative areas of the brain supports the notion that *ApoE4* carriers are more prone to develop metabolic deficiency and AD at an early age [23]. Moreover, such changes are evident even in young and presymptomatic *ApoE4* carriers [24], indicating a possible causal route of AD in *ApoE4* individuals.

The vasculature, the major metabolic exchange surface of the brain, is consistently atrophied in AD [25] and, like other brain compartments, shows reduced glucose transport [26]. These findings emphasize the multiplicity of causes and effects of lowered metabolic function such that baseline glucose metabolism and medial temporal lobe brain volumes are predictive of cognitive decline in normal older people [27]. Notably, amyloid-β interacts with insulin receptors and glucose transporters [28] and there are emerging parallels being drawn between diabetes and AD [29–32]. Indeed, amyloid formation in the pancreas is associated with β-cell loss in Type 2 diabetes [33] and a disturbance in the control of neuronal glucose metabolism, consequent to impaired insulin signaling atrophy, resembles the pathophysiology of Type-2 diabetes in non-neuronal tissue [34]. Seen together, these findings make a case for a metabolic contribution to the pathogenesis of AD.

Dietary intake and Alzheimer disease

The cerebral metabolic alterations in AD patients mentioned above are likely reflective or consequential to a number of factors including dietary intake. In this regard, a high caloric diet seemingly predates onset of disease [35–37] (Table 1). Moreover, patients who later develop AD show reduced intake of key antioxidant nutrients throughout life (Table 2).

Lipid transport is a known function of apolipoprotein E (ApoE), whose genotype has been established as a risk factor for AD [38]. Proper functioning of this protein is critical to membrane formation and the repair of nervous system injuries. Notably, a high fat diet is a risk factor in the development of AD [39, 40].

Table 1 Caloric intake of AD and control cases during three periods of adult life, ages 20–39 years, 40–59 years and 60+ years

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

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Table 2 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 (37)

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-ACarotene (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			
Yollow green vegetables	2.0	2.3	.022
Vitamin C fruit, vegetables	2.4	2.6	NS

These data strongly support the notion that free radical scavengers, here dietary antioxidants, delay or prevent the onset of AD. Reprinted from J Alzheimer's Disease 1:203–206, 1999 with permission from IOS Press

Interestingly, diet can also influence pathological markers of AD. In this regard, and associated with insulin function/resistance and metabolism, recent data indicates that Insulin-degrading enzyme (IDE), one protein with a key role in degrading amyloid-β monomer [41], is decreased in AD [42]. Providing interplay between the aforementioned high fat diets contribute to insulin resistance and lower IDE and, in animal models of AD, lead to increased amyloid deposition [43]. Altogether, these data indicate a key role that dietary influences may play in maintaining healthy brain structure and function.

Neuronal size and Alzheimer disease

To clarify the relationship between brain metabolic activity, neuronal size, and the evolution of AD, we found, in a study of oxidative damage in AD and normal aging, a strong inverse relationship between neuronal oxidative damage (8-hydroxyguanosine, a marker of nucleic acid oxidation) and neuronal size among cases of AD but not controls (Fig. 1). Additionally, we showed that, in AD cases, neuronal size is inversely correlated with the duration of the disease (Fig. 2). Previous studies found that during the progression of the disease there is a significant decrease in the size of neurons in AD when compared to controls [12, 35] and our data (Fig. 2) would tend to support this. However, while the differences in neuron size are highly correlated with oxidative damage and duration of disease among the AD cases, the increase in size is not statistically different from control cases. An alternative and more provocative possibility for this discrepancy could be explained by an antioxidant role of amyloid-β [8]. Given that amyloid-β can serve an antioxidant function, one possibility could be that amyloid-β appears as a protective mechanism in a brain inherently vulnerable to oxidative stress, which initially normalizes neuronal function and size and then through progressive accumulation alters cellular structures enough to cause neuronal shrinkage and death, as other reports have shown [6–14]. Nonetheless, it is intriguing that large neurons in AD appear most vulnerable and supporting this, we also observed that neurons from cases of Down syndrome are significantly larger than control cases (Fig. 3). Down syndrome parallels AD in lesion formation, markers of oxidative damage and most of the other changes of AD, yet these changes occur decades earlier [44]. In

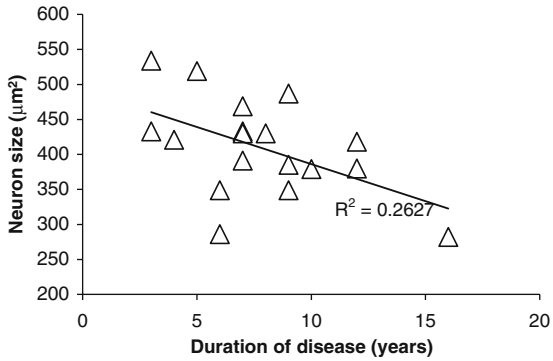

Fig. 2 In cases of AD, neuron size is inversely correlated with the duration of the disease ($P = 0.03$). This buttresses our previous finding that neuron size decreases with increasing levels of amyloid. Reprinted from *Neurochem Res* **28**:1549–1552, 2003 with kind permission of Springer Science and Business Media

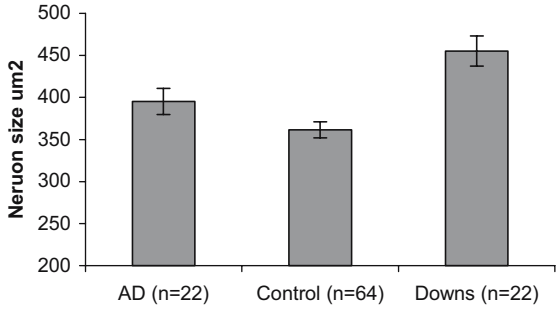

Fig. 3 Neuron size was measured in the same area of the hippocampus in AD ($n = 22$), Down syndrome ($n = 22$) and control ($n = 64$) cases. Cases of Down syndrome had significantly larger neurons than the control cases ($P = 0.00006$). While the average neuron size for the AD cases was higher than the control cases, the difference did not reach significance ($P = 0.076$; Student's t-test). Reprinted from *Neurochem Res* **28**:1549–1552, 2003 with kind permission of Springer Science and Business Media

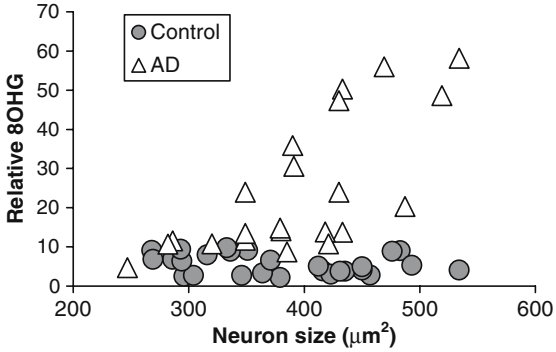

Fig. 1 In cases of AD, neuron size is directly correlated with increased levels of 8-hydroxyguanosine (8OHG) ($P = 0.002$), while control cases do not display this relationship ($P = 0.18$). Reprinted from *Neurochem Res* **28**:1549–1552, 2003 with kind permission of Springer Science and Business Media

Table 3 Comparison of previous population studies of *ApoE* allele frequencies and the cases used in this study

Diagnosis	*ApoE2* (%)	*ApoE4* (%)	Ratio *E4/E2*	Age	*n*
Control [53]	7.8	16.9	2.17	76	71
Dementia [53]	2.8	22.2	7.9	80	18
Psychiatric history [53]	12.5	10.7	0.85	71.8	28
Control (Caucasian) [54]	7	12.5	1.79	<30	939
Control (African-American) [54]	14	20	1.43	<30	696
Psychotic (Bipolar) [52]	6.3	15.1	2.39	Mean 33–67	156
Control [52]	6	12.1	2.0	Mean 43.5	91
Schizophrenic [55]	7	7.5	1.07	12–87	54
Dementia [55]	4.6	30.2	6.6	50–95	43
Control [55]	6	15.2	2.5	24–88	33
Control [56]	3.7	19.5	5.7	<18	486
Post-mortem Control[a]	23	11.5	0.5	<40	13
Post-mortem Control[a]	0	12.5		>40	8

[a] Cases obtained from the Cuyahoga County Coroner Office, Cleveland, Ohio

As expected, the populations with dementia display the highest frequency of εE4 and the highest ratio of εE4/E2, 6.6 and 7.9. The 6 control populations, not including our data, have a E4/E2 ratio from 1.43–5.7, with the average frequency of E4 being about 2.5 times greater than E2. Interestingly, in 2 of the 3 previous studies of ApoE genotype and psychotic behavior, the ratio of E4/E2 is 1.07 and 0.85. Our population study displayed an even greater frequency of ApoE2. Of the 6 cases carrying the ApoE2 allele, 3 committed suicide. In other words, ApoE2 may be a risk factor for mental illness

addition, Down syndrome cases also experience neuronal loss and have similar genetic risk factors [35].

To determine the relationship between neuronal size, AD, and *ApoE* genotype, we determined the *ApoE* genotype of the control cases to identify those at risk of AD. Control cases (ages 42–85 years) with at least one *ApoE4* allele had a cross sectional area significantly larger compared to other controls lacking *ApoE4*. In contrast, young controls (ages 20–40 years) show no correlation between neuronal size and *ApoE* genotype. These findings further suggest that the *ApoE4* allele may play a role during aging and disease progression that influences neuron size. As such, one possibility is that the alteration of lipid or axonal transport of *ApoE4* carriers may be a cause of the accumulation of organelles [45] within neurons early in the disease, leading to a neuronal enlargement and then to neuronal shrinkage and death during the progression of AD. Supporting this idea, while AD is associated with a significantly reduced size of the Golgi apparatus, individuals with mild cognitive impairment (MCI) show substantially increased size [46]. Another possibility is that, in order to compensate for metabolic dysfunction produced by, for example, *ApoE4* status, organelles associated with metabolism undergo a compensatory enlargement that may then lead to further damage and subsequent shrinkage and death of the neuron in more advanced stages of AD.

As a side note, related to *ApoE* genotype, an interesting trend was apparent when analyzing young controls. Out of 13 cases under the age of 32, six carried an *ApoE2* allele. Most of the genetic studies in aging and AD focus on the increase in *ApoE4* [47] and some studies [48–50], but not all [51], have noted that *ApoE2* is protective for AD. We compared our relatively small sample population with published studies and determined that the frequency of *ApoE2* was much higher than those reported for other control populations (Table 3). Of note was the fact that our samples were obtained postmortem and of the 6 cases carrying an *ApoE2* allele, 3 committed suicide and 2 succumbed to violence. In previous studies, the frequency of *ApoE2* was increased in cases with psychosis [24, 52]. Our results fall into this category-perhaps, *ApoE2* genotype is a determinant of susceptibility to violent death.

Conclusion

While the data presented above do not illustrate a causal relationship between neuronal size and AD development and progression, these changes occur due to metabolic alterations that appear early in the onset of the disease. Although there is insufficient data to know if diet can be protective for neurodegeneration, or, instead, is a surrogate marker of other lifestyle patterns promoting general health, it is well known that proper nutrition and a healthy diet are essential for maintaining overall good health and, therefore, can be beneficial to AD patients. These findings allow the development of new studies focused on the events associated with the onset of the disease process such as diet, glucose metabolism, and neuronal size. Those

studies could be critical for the understanding of basic mechanisms underlying AD pathophysiology and, consequently, the development of new therapeutic strategies.

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