Mitochondria, Diabetes, and Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease as well as the leading cause of dementia (1,2). Identification of disease-causing mutations in the amyloid precursor protein, presenilin 1, and presenilin 2 has unraveled the molecular basis of some forms of familial AD, but the etiology and pathogenesis of sporadic AD remain elusive and controversial. Epidemiological data suggest that diabetes increases the risk of developing AD (2–4). These data are corroborated by clinical and laboratory findings. Indeed, diabetic subjects show signs of cognitive dysfunction, leukoariosis, and more severe hippocampal atrophy than control subjects (5). In addition, neuritic plaques and neurofibrillary tangles, the pathological hallmarks of AD, accumulate more abundantly in the brains of diabetic patients relative to control subjects. The association between diabetes and AD pathology seems even stronger among carriers of the apolipoprotein E $\varepsilon 4$ allele, a variant that by itself carries an increased risk for AD (6).

The hyperglycemia and hyperinsulinemia that may accompany the preclinical syndrome of type 2 diabetes may play a role in the pathogenesis of AD. In particular, elevated levels of insulin, which crosses the blood-brain barrier, may compete with amyloid β for the insulin-degrading enzyme. This enzyme has a major role in clearance of both insulin and amyloid β peptide, the latter being the major component of neuritic plaques in the AD brain (7).

Several lines of evidence support involvement of mitochondria in the pathogenesis of AD. Mitochondria are highly dynamic organelles that play an essential role in the production of ATP by oxidative phosphorylation and cell survival (8). Mitochondria undergo continuous fusion and fission that regulate their shape, distribution, and function (9). Decline in the number of normal-appearing mitochondria, reduced activity of complex IV (cytochrome c oxidase) of the electron transport chain and of other mitochondrial enzymes, as well as defects in mitochondrial dynamics, all occur in AD neurons (10,11). The impaired balance in mitochondrial fission and fusion may represent a likely mechanism for mitochondrial dysfunction and secondary neuronal insult in the AD brain (11).

In this issue of *Diabetes*, Carvalho et al. (12) investigated the hypothesis that mitochondria may represent the functional link between diabetes and AD. They evaluated the effect of sucrose-induced metabolic alteration on the brain mitochondria of wild-type (WT) mice subjected to 20% sucrose-sweetened water for 7 months. These data were compared with those observed in the brains of WT mice and of triple transgenic (3xTg)-AD mice. Simply comparing the experimental animals, the investigators detected an increase in HbA_{1c} in the sucrose-treated mice and 3xTg-AD mice. Mitochondria from both groups of animals showed similar functional and structural abnormalities. These consisted of defects in respiratory chain and phosphorylation system leading to decreased ATP production, abnormal calcium buffering, impaired antioxidant defenses, and disrupted mitochondria cristae and membranes. In addition, sucrose-treated mice showed elevated levels of amyloid β, especially in the cortex.

These findings highlight how mitochondrial dysfunction and accumulation of amyloid β observed in a mouse model of diabetes are similar to those observed in a mouse model of AD. The data strengthen the scientific link between AD and diabetes identified by epidemiological and clinical studies and by previous experiments (7). In addition, the current study corroborates the role of mitochondrial dysfunction in the pathogenesis of AD and provides further evidence that AD is not only the result of misfolded amyloid β peptide and accumulation of phosphorylated τ, but also the product of increased oxidative stress and reduced energy metabolism. Of interest, a recent study (13) has shown that mitoquinone mesylate, a mitochondria-targeted antioxidant that can cross the blood-brain barrier and concentrate in mitochondria, can prevent cognitive decline in 3xTg-AD mice. This drug also reduces the oxidative stress and amyloid β accumulation in the brain of these animals. It would be of interest to see if mitoquinone would have a protective effect on the neurons of diabetic mice by ameliorating oxidative stress-mediated disease and preventing amyloid β accumulation in the brain. Another interesting point, although not new, is the detection of significantly reduced mitochondrial transmembrane potential ($\Delta\Psi_m$) in sucrose-treated mice and in 3xTg-AD mice. It has been suggested that the direction of mitochondrial transport is correlated with mitochondrial potential; therefore mitochondria with high membrane potential undergo anterograde transport, while depolarized mitochondria return to the soma where they are degraded or repaired (14). The detection of low $\Delta\Psi_m$ could also have a role in the axonal dysfunction and etiology of diabetic peripheral neuropathy.

Although mitochondrial damage has been associated with the pathophysiology of many disorders, one should be cautious about qualifying its role as a disease-causing mechanism. While mitochondrial dysfunction secondary to genetic defects in proteins directly affecting mitochondrial function is the culprit of the pathogenetic mechanism in some cases, in many other cases it represents only a secondary phenomenon. Huntington disease is a classical example. Huntington disease is a neurodegenerative disorder caused by abnormal polyglutamine expansion in huntingtin. The mutant huntingtin enhances the enzymatic activity of dynamin-like protein 1, a protein involved in mitochondrial fission, inducing mitochondrial fragmentation and loss of

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DOI: 10.2337/db12-0209

See accompanying original article, p. 1234.

bidirectional mitochondrial transport (15). Mitochondrial dysfunction can therefore be the end point of a chain of events even in diseases with known molecular defects unrelated to mitochondria. The relevance of mitochondrial dysfunction is more difficult to interpret in diseases with unclear etiology. Nevertheless, the identification of mitochondrial dysfunction in a specific disease might help our understanding of disease mechanisms, potentially leading to novel therapeutic avenues, even if mitochondrial dysfunction was not the primary cause of the disease.

ACKNOWLEDGMENTS

This work was supported by the Mayo Clinic Center for Translational Science Activities through grant number UL1 RR024150 from the National Institutes of Health/National Center for Research Resources.

No potential conflicts of interest relevant to this article were reported.

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