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Editorial
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Mitochondrial Dysfunction, The Common Denominator for Alzheimer's Disease and Diabetes

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Editorial

Alzheimer's disease (AD) and diabetes mellitus are chronic disorders associated with aging. They represent a looming crisis with increasing health care and economic demand worldwide. Extensive literature exists linking the development of AD to diabetes including dysregulated glucose metabolism and mitochondrial dysfunction. This review summaries evidence demonstrating mitochondrial dysfunction and cellular bioenergetics plays a central role in the etiology of AD. Additionally, the review also discusses the possibility of protecting mitochondrial function as an alternative therapeutic approach for treating AD.

Mitochondrial Dysfunction in Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of dementia characterized by progressive loss of memory and cognition [1]. The two pathological hallmarks of AD are formation of amyloid plaque from aggregated amyloid-β-peptide (Aβ) and formation of neurofibrillary tangles from hyperphosphorylated tau. The Alzheimer's Association report pointed out that one in nine people over the age of 65 has AD and it represents a looming crisis with increasing health and economic demand worldwide [1]. Despite the identification of mutations related to familial AD (FAD), the cause of sporadic AD remains elusive and controversial [2,3]. Similarly, Type 2 Diabetes Mellitus (T2DM), another prevalent disorders characterized by hyperglycemia, insulin resistance and relative insulin deficiency, is associated with obesity and often aging [4,5].

Epidemiological studies have indicated that AD and T2DM represent interdependent risk factors for each other [2,6-8]. Using global metabolomics profiling, Trushina *et al.* [9] demonstrated that metabolic changes associated with obesity and diabetes were present in plasma of AD patients. Further, impaired glucose tolerance and insulin resistance, the major pathologies of diabetes, parallel worsening of dementia in diabetic [10] and AD [11-13] patients implying a bidirectional relationship between the diseases. The level of clinical debility in AD correlates closely with the degree of reduced brain metabolism, which precedes the onset of the overt clinical symptoms by decades [14,15]. Diminished brain metabolism in clinical AD is a prominent abnormality contributing to hyperphosphorylation of tau and Aβ accumulation [16,17]. Multiple underlying mechanisms have emerged that link the development of diabetes with AD including abnormal protein processing, impaired insulin signaling, dysregulated glucose metabolism and mitochondrial dysfunction [9,18-22]. Epidemiological, clinical and experimental studies have demonstrated that defective bioenergetics, altered Krebs cycle and mitochondrial dysfunction play a central role in the development of AD, parallel to the accumulation of Aβ, and represent a functional link between AD and diabetes [2,9,23,24]. Mitochondria dysfunction [19-21] have been proposed as an early event in the etiology of both disorders [18,22]. Owing to the profound socioeconomic impact of AD and diabetes, understanding the mechanisms that interconnect these diseases is essential for the development of novel therapeutic interventions.

Mitochondria are the master regulators of cellular energetic homeostasis [25,26]. Mitochondrial bioenergetics deficit increases reactive oxygen species (ROS) production, which induce cellular damage [27] contributing to neurodegeneration and cell death [28,29]. The energy metabolism, Krebs cycle and mitochondrial function were significantly affected in patients with mild cognitive impairment (MCI) and AD [9] and in multiple animal models of FAD [30-33] suggesting that loss

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of bioenergetics plays a central role in the etiology of AD. In support of this, Bubber *et al.* [23] demonstrated that loss of mitochondrial enzymatic activity in the brain tissue isolated from autopsy-confirmed AD patients correlated with severity of dementia. Moreover, sucrose diet can induce mitochondrial abnormalities in wild-type (WT) mice brain similar to those found in transgenic mice expressing FAD genes [34]. Additionally, sucrose diet also increased production of amyloid beta (Aβ) peptides in WT mice [34], suggesting that conditions leads to diabetes can exacerbate the onset of AD. Conversely, similar observations were found in animal model of FAD, where declined mitochondrial function was associated with increased glucose and insulin intolerance, age and Aβ deposition [34-37].

The shared mechanism between AD and diabetes has motivated many to explore the feasibility of common pharmacotherapy for T2DM and AD [38-43]. One of the most commonly prescribed diabetic drugs is metformin. Metformin is an orally active biguanide that helps to control blood glucose level. While the mechanisms of action are not completely understood, studies have shown that patients with T2DM and AD receiving metformin have a lower rate of cognitive decline [40,44,45]. Notably, other studies showed that metformin could increase intracellular Aβ level and T2DM patients under long-term treatment of metformin have increased risk of AD [41,46]. These controversial studies suggest that there is considerable challenge to develop drug for AD. A preclinical study by Zhang *et al.* [31] reported a tricyclic pyrone compound, CP2 that has dual effect on both Aβ and mitochondria. CP2 improves cognitive functions in multiple FAD mouse models through direct binding to Aβ. More importantly, CP2 also inhibit the function of mitochondrial complex I (NADH: ubiquinone oxidoreductase) by directly bind to the flavin mononucleotide (FMN) redox site. This action limits initial entry of electrons into the electron transport chain system thus prevents induction of oxidative stress or inflammation. To date, numerous attempts to treat AD by targeting Aβ have failed in human clinical trials. Thus, Zhang *et al.* [31] study represents an alternative therapeutic approach through interfering cellular bioenergetics and metabolism.

Even though AD and T2DM are traditionally considered independent disorders and are treated separately, extensive studies have showed that the disorders shared mitochondrial dysfunction as the common denominator. Therefore, therapeutic approaches that protect mitochondrial dynamics and function and simultaneously reduce Aβ deposition could delay the onset of the disease or reverse/slow down the disease progression in both AD and diabetes.

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