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REVIEW

MOLECULAR LINKS BETWEEN ALZHEIMER'S DISEASE AND DIABETES MELLITUS

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Abstract—Substantial epidemiological evidence shows an increased risk for developing Alzheimer's disease (AD) in people with diabetes. Yet the underlying molecular mechanisms still remain to be elucidated. This article reviews the current studies on common pathological processes of Alzheimer's disease and diabetes with particular focus on potential mechanisms through which diabetes affects the initiation and progression of Alzheimer's disease. Impairment of insulin signaling, inflammation, oxidative stress, mitochondrial dysfunction, advanced glycation end products, APOEε4 and cholesterol appear to be important mediators and are likely to act synergistically in promoting AD pathology.

Key words: Alzheimer's disease, diabetes, molecular links.

Contents

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Abbreviations: AD, Alzheimer's disease; APP, amyloid β precursor protein; BACE1, β-site APP-cleaving enzyme 1; Aβ, amyloid β protein; hIAPP, human islet amyloid polypeptide; IDE, insulin-degrading enzyme; IGF, insulin-like growth factor; GSK3β, glycogen synthase kinase 3β; NSAID, non-steroidal anti-inflammatory drug.

INTRODUCTION

It is estimated that 36 million people worldwide are afflicted by Alzheimer's disease (AD), with a global cost of $604 billion in 2010 alone (Wimo and Prince, 2010). Unfortunately, the currently available treatment for AD could only, at best, provide symptomatic benefit rather than cure to the disorder. The lack of effective treatment is mainly due to unelucidated etiology of the disease. A number of epidemiological studies revealed an elevated risk for developing AD in diabetic patients. Many studies have tried to investigate the mechanism underlying the association with the hope of finding effective prevention and treatment of AD. In this article, we first briefly reviewed the current understanding of AD and diabetes and the clinical association of the two disorders, and then outlined the emerging mechanisms that potentially mediate or modulate the processes.

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by progressive memory deficit and neuronal loss. The pathological features of AD include extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs) and neuronal loss. Amyloid plaques consist mainly of aggregated amyloid β protein (Aβ), which derives from sequential cleavage of the amyloid β precursor protein (APP) by β-site APP cleavage enzyme 1 (BACE1) and the γ-secretase complex (Sun et al., 2012). A major component of NFT is abnormally hyperphosphorylated tau, a microtubule-associated protein, predominantly localized in neuronal axons (Johnson and Stoothoff, 2004).

AD can be caused by autosomal dominant gene mutations in *APP* (Goate et al., 1991), *presenilins 1* (PS1) (Sherrington et al., 1995), and *presenilins 2* (PS2) (Levy-Lahad et al., 1995; Rogaev et al., 1995) which promote the development of cerebral Aβ deposits. Yet, majority of the AD cases are sporadic and do not exhibit clear familial or genetic clustering (Rocchi et al., 2003).The cause of sporadic AD still remains unknown, and many associated risk factors have been identified (Ballard et al., 2011). Among these, diabetes stands as a strong risk factor for AD.

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Diabetes mellitus

Diabetes is a complex metabolic disorder characterized by chronic hyperglycemia and associated with macrovascular and microvascular complications. Depending on the severity of the disorder, the clinical presentations range widely from being asymptomatic to polyuria and polydipsia to ketoacidosis or coma. According to the World Health Organization's report released in September 2012, 347 million people worldwide are currently suffering from diabetes mellitus (WHO, 2012). Two major forms of diabetes, classified by etiology, are type 1 diabetes which is characterized by an absolute deficiency in insulin resulting from autoimmune destruction of pancreatic β-cells, and type 2 diabetes which features combinations of decreased insulin secretion and insulin resistance (American Diabetes Association, 2012). Type 2 diabetes accounts for about 90% of all the diabetes cases (WHO, 2012). Substantial epidemiological evidence suggests that both type 1 and type 2 diabetes are strongly associated with cognitive impairment (Strachan et al., 1997; Stewart and Liolitsa, 1999; Brands et al., 2005; Cukierman et al., 2005).

THE LINK BETWEEN DIABETES AND AD

Accumulating epidemiological evidence shows an increased risk of Alzheimer's disease in people with diabetes. In a systematic review of longitudinal population-based studies that compare the incidence of dementia between diabetic and non-diabetic groups, Biessels et al. reported an increase in the risk of AD of 50–100% in diabetic individuals with no obvious relation to ethnic origins (Biessels et al., 2006). Similarly, in a more recent review, Kopf et al. also reported an elevated risk of AD in people with diabetes (Kopf and Frolich, 2009). The report also pointed out that studies with larger sample size, ascertainment of early diabetes and strict diagnosis for dementia subtype are prone to show a positive association between the two diseases.

On the other hand, the prevalence of diabetes and impaired fasting glucose (IFG) is greater in AD versus non-AD group, with 81% of the AD patients exhibiting either IFG (fasting glucose concentration 110–125 mg/dL) or diabetes (fasting glucose concentration $\geqslant$ 126 mg/dL) in a community-based controlled study (Janson et al., 2004).

POTENTIAL MECHANISMS UNDERLYING THE ASSOCIATION

Amyloidogenesis

Generation of amyloid peptides and the aggregation of abnormally folded proteins is a shared pathological characteristic in diabetes and AD (Chiti and Dobson, 2006). Extracellular amyloid plaques, which are composed of insoluble aggregation of Aβ, is a prominent pathological feature of AD. The major protein component of amyloid plaques, Aβ, is a 4-kDa peptide produced from sequential cleavage of APP. Aβ can oligomerize into larger soluble assemblies and it can also undergo conformational changes and arrange into cross-β-sheet units, forming amyloid fibrils in the senile plaques (Kirkitadze and Kowalska, 2005). The amyloid hypothesis believes pathological Aβ assemblies as the central and initiating event in the disease process (Karran et al., 2011). While previous studies focused on the neurotoxicity of aggregate fibrillar Aβ, accumulating evidence has demonstrated the significance of soluble Aβ assemblies in neuropathology such as the impairment of long-term potentiation and neuronal death (Lambert et al., 1998; Walsh et al., 2002; Lesne et al., 2006; Townsend et al., 2006; Shankar et al., 2008). Moreover, soluble Aβ oligomers appear to be better correlated with dementia and synaptic loss than deposited Aβ in plaques (Lue et al., 1999; McLean et al., 1999).

Analogous to amyloid plaques in AD brains are the islet amyloid deposits in the pancreas of diabetic patients. Ninety percentage of diabetic patients have pancreatic islet amyloid which is associated with decreased β-cell mass (Clark et al., 1988).The islet amyloid is the pathological aggregation of amylin or human islet amyloid polypeptide (hIAPP) which has 37 amino acids (Cooper et al., 1987; Westermark et al., 1987) and is derived from an 89-amino acid precursor by proteolytic processing (Sanke et al., 1988). Both the molecular structure and morphology of hIAPP fibrils resemble those of Aβ fibrils in AD (Luca et al., 2007). Under physiological conditions, hIAPP is coexpressed and cosecreted with insulin by pancreatic β-cells (Leffert et al., 1989; Butler et al., 1990; Kahn et al., 1990). The exact physiological function of hIAPP is unknown and it seems to be able to inhibit glucose-stimulated insulin secretion (Ohsawa et al., 1989). In mice that lacks hIAPP, insulin secretion is enhanced and glucose tolerance is improved (Gebre-Medhin et al., 1998). Like Aβ, hIAPP can form early assembly intermediates (Porat et al., 2003; Green et al., 2004). Moreover, just like soluble Aβ oligomers can cause neuronal loss, soluble hIAPP oligomers are shown to induce β-cell apoptosis (Janson et al., 1999; Konarkowska et al., 2006; Meier et al., 2006). It has been suggested that the two exert toxicity by similar mechanisms (Kawahara et al., 2000; Anguiano et al., 2002; Lim et al., 2008).

Insulin signaling impairment and insulin degrading enzyme

Insulin, insulin receptor and its substrates are present throughout the central nervous system (CNS) (Baskin et al., 1988; Adamo et al., 1989). Insulin in the brain controls food intake and body weight (Woods et al., 1979; Schwartz et al., 1992; Baskin et al., 1999). Insulin is also involved in the regulation of neurotransmitter release and synaptic plasticity (Jonas et al., 1997; Wan et al., 1997; Wang and Linden, 2000; Skeberdis et al., 2001; Ahmadian et al., 2004), and hence may play an important role in learning and memory (Zhao and Alkon, 2001). In fact, rats with intracerebroventricular injection of streptozotocin which depletes insulin by destroying pancreatic β cells developed long-term deficits in cognitive behavior (Biessels et al., 1998; Lannert and