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Bidirectional interactions between diabetes and Alzheimer's disease

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ABSTRACT

Clinical studies have indicated that diabetes is associated with Alzheimer's disease (AD) and neurodegeneration. However, the mechanisms underlying this association have not been fully elucidated. Diabetes causes neurodegeneration by inducing changes in vascular function and structure, glucose metabolism, and insulin signaling, as well as by modifying β−amyloid (Aβ)/tau metabolisms. In turn, AD influences systemic glucose metabolism by inducing behavioral changes, memory disturbances, hypothalamic dysfunction, frailty and possibly plasma/peripheral Aβ level changes. Hypoglycemia, one of the major conditions encountered during the treatment of patients with diabetes, may also contribute to neurodegeneration. Through this vicious circle, diabetes and AD may cooperate to cause neurodegeneration. Various molecular, cellular, inter-organ, physical and clinical factors might contribute to the bidirectional interactions between diabetes and AD. Explorations of a key factor that underlies the bidirectional interactions, "Factor X", could lead to the development of a potential therapeutic target for neurodegeneration. Factor X should fulfill the following equation: neurodegeneration equals Aβ levels multiplied by Factor X.

Contents

1. Introduction

Emerging evidence indicates that diabetes increases the risk of Alzheimer's disease (AD) and neurodegeneration. However, the mechanisms by which diabetes modifies AD and the mechanisms underlying diabetes-associated peripheral neuropathy remain unclear (Sato and Morishita, 2013b, 2015). Insulin resistance in midlife is associated with neurodegeneration surrounding senile plaques (Matsuzaki et al., 2010), although retrospective studies have suggested that the magnitude of senile plaques is comparable between

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individuals with AD and diabetes and those with AD and without diabetes (Kalaria, 2009). Indeed, diabetes alters brain structure and function through various mechanisms, and its contributions to dementia vary among patients (Sato and Morishita, 2014). Furthermore, a dual effect has been observed. In addition to the effect of diabetes on AD, the effects of AD on diabetes and systemic metabolism may further contribute to the tendency of these two seemingly unrelated diseases to exacerbate one another.

2. Diabetes and neurodegeneration

2.1. Diabetes and cognitive decline

Diabetes/impaired glucose tolerance is associated with mild cognitive impairment (MCI) (Roberts et al., 2014b) and with the progression to dementia in patients with MCI (Morris et al., 2014). Higher HbA1c levels are a risk factor for cognitive dysfunction (West et al., 2014) and for behavioral and psychological symptoms (Sakurai et al., 2014). Importantly, in a study of patients with familial AD harboring presenilin mutations, individuals with diabetes exhibited greater cognitive decline after the onset of AD (Aguirre-Acevedo et al., 2016). In patients with sporadic AD, patients with diabetes and substantial AD pathological changes exhibited lower cognitive function than patients with the pathological changes alone (Abner et al., 2016). Even among individuals without AD, cognitive function decreases more rapidly in patients with diabetes than in the controls (Weinstein et al., 2015; Redondo et al., 2016). In Holmes and colleagues' assessment of patients with diabetes who presented with hypoglycemia and hyperglycemia induced by an artificial insulin/glucose infusion, cognitive function was delayed when the patients' glucose levels were altered (Holmes et al., 1983).

According to observational studies, the use of anti-diabetic treatments is associated with a reduced risk of dementia (Heneka et al., 2015) (Ng et al., 2014), but other studies did not report similar observations (Moore et al., 2013). In the randomized Memory in Diabetes (MIND) sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, intensive glycemic control had no effect on cognitive function (Launer et al., 2011) (Strachan and Price, 2014). Intensive treatment increases the incidence of hypoglycemia (McCoy et al., 2016). Indeed, hypoglycemia is associated with cognitive impairment and dementia in elderly patients with diabetes (Whitmer et al., 2009; Yaffe et al., 2013; Pilotto et al., 2014). Therefore, diabetes treatments are considered to prevent hyperglycemia and hypoglycemia, improve cognitive performance and aid in preventing dementia.

2.2. Diabetes and brain atrophy

Diabetes reduces brain volume (Sato and Morishita, 2014), including the volumes of the hippocampus (Kerti et al., 2013; Moran et al., 2013; Roberts et al., 2014b; Hirabayashi et al., 2016), gray matter (Garcia-Casares et al., 2014; Li et al., 2016) and white matter (Moran et al., 2013). Gray matter loss occurs in the frontal and temporal lobes and in the anterior cingulate cortex (Moran et al., 2013; Garcia-Casares et al., 2014; Roberts et al., 2014b; Erus et al., 2015), whereas white matter loss is also observed in the adjacent regions (Moran et al., 2013). Even in young adults, hyperglycemia is associated with brain atrophy (Weinstein et al., 2015). In animal models, neurodegeneration has been shown to be caused by the disturbance of glucose metabolism with substantial Aβ levels in mice overexpressing mutant amyloid precursor protein (APP) crossed with *ob/ob* mice (Takeda et al., 2010). Moreover, a high-fat diet (Thiebaud et al., 2014), glucose transporter 1 (GLUT1) deficiency (Winkler et al., 2015), over-activation of the energy sensor AMP-activated protein kinase (AMPK) (Mairet-Coello et al., 2013), and disruption of mammalian target of rapamycin (mTOR) signaling (Perluigi et al., 2015) have been shown to cause neurodegeneration.

2.3. Diabetes and cerebrovascular changes

Diabetes increases vascular changes in the brain, heart, kidney and other organs. Vascular changes are concomitantly observed more frequently in the brains of patients with AD and diabetes than in patients with AD without diabetes (Kalaria, 2009). Compared to non-diabetes conditions, diabetes increases cerebral infarct volumes by more than 2-fold (Tanizaki et al., 2000; Arvanitakis et al., 2006; Roberts et al., 2011). Diabetes increases atherosclerosis in the brain by inducing insulin resistance and hyperglycemia (Schmidt et al., 1995; Vicent et al., 2003; Piga et al., 2007). Insulin resistance reduces nitric oxide production (Vicent et al., 2003), which alters the blood vessel reflex and increases the levels of adhesion molecules, which recruit monocytes to the vessel wall. Monocytes penetrate deep into the blood vessel wall and cause inflammation, resulting in arteriosclerosis. Advanced glycation end-products (Schmidt et al., 1995) or high glucose levels (Piga et al., 2007) increase the expression of vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells and subsequent inflammation and reduce NO production to exacerbate arteriosclerosis. Moreover, half of patients with diabetes are hypertensive (Sowers et al., 2001; Sowers, 2013), which accelerates vascular injury in the brain (Bouchi et al., 2010).

2.4. Diabetes, brain glucose metabolism and insulin signaling

In humans, diabetes/hyperglycemia are associated with brain hypometabolism (Roberts et al., 2014a; Ishibashi et al., 2016; Li et al., 2016). Changes in the distribution pattern of [^{18}F]-fluorodeoxyglucose (F-FDG) depend on the plasma glucose levels, and an AD-like pattern can appear in patients with hyperglycemia (Roberts et al., 2014a; Ishibashi et al., 2016). In an Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, whole brain F-FDG uptake was lower in patients with MCI and diabetes than in patients with MCI without diabetes (Li et al., 2016), indicating that diabetes modifies brain glucose metabolism in the pre-dementia state. Insulin signaling also occurs in the brain (Sato et al., 2011). Brain insulin resistance has been reported in patients with AD (Talbot et al., 2012) and in animal models of diabetes (Takeda et al., 2010; Sato et al., 2011; Morales-Corraliza et al., 2016; Sajan et al., 2016). The expression of insulin-like growth factor-1 (IGF1)-binding protein, an inhibitor that binds IGF1, is increased in patients with peripheral diabetic neuropathy, and inhibition of IGF1 by overexpressing IGF1-binding protein in mice resulted in the development of motor axonopathy and sensory deficits (Rauskolb et al., 2016), indicating that the dysregulation of insulin/IGF signaling might also contribute to CNS neurodegeneration induced by diabetes. The molecular mechanism underlying the link between insulin signaling and neurodegeneration warrants further study.

2.5. Diabetes and AD pathology

2.5.1. Aβ

Diabetes/hyperglycemia modify Aβ accumulation in the brains of wild type animals (Sparks et al., 1994) and animal models of AD (Refolo et al., 2000; Ho et al., 2004; Takeda et al., 2010). Hyperglycemia may increase Aβ production by increasing the synaptic release of Aβ (Macauley et al., 2015) or modulating APP processing and metabolism (Son et al., 2012) through molecules such as beta secretase-1 (BACE1) (Guglielmotto et al., 2012), glycogen synthase kinase-3β (GSK3β) (Phiel et al., 2003; Sereno et al., 2009; Sofola et al., 2010; Jaworski et al., 2011), or insulin-degrading enzymes