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Diabetes augments cognitive dysfunction in chronic cerebral hypoperfusion by increasing neuronal cell death: Implication of cilostazol for diabetes mellitus-induced dementia

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ABSTRACT

Many patients with diabetes are at increased risk of cognitive dysfunction and dementia. Diabetes mellitus is a vascular risk factor that may increase the risk of dementia through its associations with vascular dementia. We tested whether cognitive impairment could be exacerbated in combined injury using a rat model of chronic cerebral hypoperfusion with diabetes. We also determined whether a potent inhibitor of type III phosphodiesterase could prevent the cognitive decline caused by this combined injury.

We used Otsuka Long–Evans Tokushima Fatty (OLETF) rats as a model of type II diabetes (T2DM) and Long–Evans Tokushima Otsuka (LETO) rats as a control. Chronic cerebral hypoperfusion was modeled by permanent bilateral common carotid artery occlusion (BCCAO). At 24 weeks, the non-diabetic and T2DM rats were randomly assigned into groups for the following experiments: analysis I (1) sham non-diabetic rats ($n = 8$); (2) hypoperfused non-diabetic rats ($n = 9$); (3) sham T2DM rats ($n = 8$); (4) hypoperfused T2DM rats ($n = 9$); analysis II- (1) sham T2DM rats without treatment ($n = 8$); (2) cilostazol-treated T2DM rats ($n = 8$); (3) hypoperfused T2DM rats ($n = 9$); and (4) hypoperfused T2DM rats and cilostazol treatment ($n = 9$). The rats were orally administered cilostazol (50 mg/kg) or vehicle once a day for 2 weeks after 24 weeks. Rats performed Morris water maze tasks, and neuronal cell death and neuroinflammation were investigated via Western blots and histological investigation.

Spatial memory impairment was exacerbated synergistically in the hypoperfused T2DM group compared with the hypoperfused non-diabetic group and sham T2DBM group ($P < 0.05$). Compared with the control group, neuronal cell death was increased in the hippocampus of the hypoperfused T2DM group. Cilostazol, a PDE-3 inhibitor, improved the memory impairments through inhibition of neuronal cell death, activation of CREB phosphorylation and BDNF expression in the hypoperfused T2DM group.

Our experimental results support the hypothesis that there are deleterious interactions between chronic cerebral hypoperfusion and T2DM. That is, metabolic diseases such as diabetes may exacerbate cognitive impairment in a rat model of vascular dementia. We also suggest that surprisingly, the phosphodiesterase III inhibitor, cilostazol may be useful for the treatment of cognitive impairment in diabetes mellitus-induced dementia. In conclusion, diabetes can aggravate cognitive dysfunction in vascular dementia, and PDE-3 inhibitors, such as cilostazol, may form the basis of a novel therapeutic strategy for diabetes-associated cognitive impairment or vascular dementia.

Introduction

The incidences of Alzheimer's disease (AD) and diabetes mellitus (DM) (Darsalia et al.) are increasing as the population ages. Many recent epidemiologic studies have shown that DM is a potential risk factor for AD development (Arvanitakis et al., 2004; Breteler, 2000; Takeda et al., 2011). Patients with type 2 DM (T2DM) were found to have twice the

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Table 1
Body weight and glucose level before treatment with cilostazol.

	LETO		OLETF	
	CON (n = 6)	BCCAO (n = 8)	CON (n = 6)	BCCAO (n = 8)
12 weeks				
Body weight (g)	360.9 ± 10.1		410.8 ± 6.2[a]	
Glucose (mg/dL)	103.6 ± 5.6		165.8 ± 2.9[a]	
Total cholesterol (mg/dL)	92.3 ± 5.2		198.3 ± 12.2[a]	
Triglyceride (mg/dL)	47.9 ± 3.1		136.9 ± 10.4[a]	
24 weeks				
Body weight (g)	420.8 ± 12.9	405.7 ± 3.7	601.2 ± 5.0[a]	581 ± 2.4[a]
Glucose (mg/dL)	119.8 ± 4.4	122.9 ± 5.3	207.1 ± 2.6[a]	218.7 ± 4.9[a]

[a] $P < 0.05$, versus LETO.

risk of developing AD and other types of dementia in comparison with those who had no problems with blood sugar control. The dementia risk remains high with other pathological conditions such as high blood pressure, high cholesterol, and smoking, which are also known to increase the risk of AD. This association may be explained by the DM-mediated cerebrovascular damage affecting cognition. It is known that subjects with a medical and family history of DM have very high incidences of vascular dementia (Luchsinger et al., 2001; Ott et al., 1996, 1999). Recently, it was recognized that cerebrovascular dysfunction plays an important role in various types of dementia, including vascular dementia and AD (Iadecola, 2010). However, it has also been determined that diabetic conditions, independent of vascular factors, may affect the pathogenesis of AD in terms of cognitive decline (Ott et al., 1999; Takeda et al., 2011). These findings highlight the important role of metabolic conditions in the pathogenesis of AD and vascular dementia. However, the mechanism underlying the association between DM and dementia remains unclear.

There is growing evidence that T2DM is associated with poor neurocognitive outcomes. More specifically, it is well documented that working, perceptual, episodic, and semantic memories, as well as visuospatial ability, are impaired in patients with diabetes. Recently, it was also reported that Aβ autoantibody serum levels are increased in T2DM (Kim et al., 2010).

Chronic cerebral hypoperfusion by bilateral common carotid artery occlusion (BCCAO) has been used as an animal model of vascular dementia (Choi et al., 2011a; Farkas et al., 2002), in which a moderate and persistent reduction in cerebral blood flow induces memory impairment and the development and progression of dementia. DM, one of the most common chronic diseases, includes pathological changes such as vascular damage. Recently, there has been a growing interest in the effects of diabetes on the brain with increasing age. However, few prospective studies have examined the association between DM and the incidence of vascular dementia. Some clinical findings indicate that subjects with DM have an increased risk of AD, not finding this

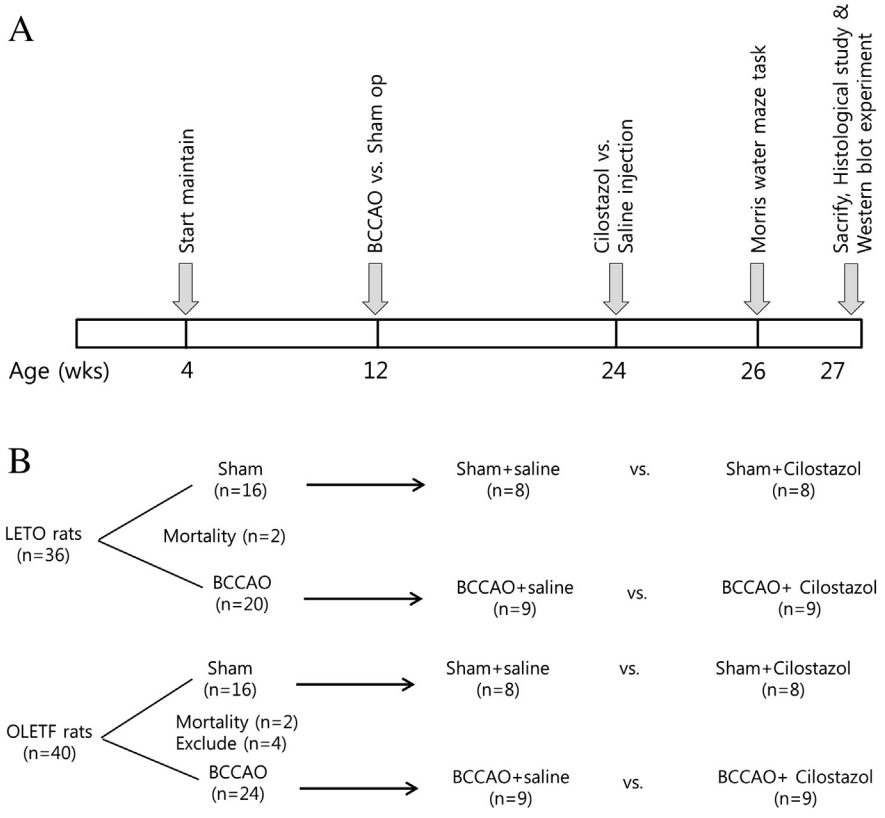

Fig. 1. Table indicating allocations for each group (A) and the timeline of the experiment (B).