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Antidiabetics drugs in treatments Alzheimer's disease (AD)

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Abstract

Epidemiological and basic science evidence suggest a possible shared pathophysiology between type 2 diabetes mellitus (T2DM) and Alzheimers disease (AD). It has even been hypothesized that AD might be ‘type 3. We examined the association between diabetes-related factors and pathology of Alzheimer disease (AD) to evaluate how diabetes affects the pathogenic process of AD .and how the treatment of (AD) type 2 diabetes mellitus (T2DM) can affect on Alzheimers disease (AD) patients. This study included specimens from a series of 135 autopsies of residents of the town of Hisayama in Fukuoka prefecture (74 men and 61 women) performed between 1998 and 2003, who underwent a 75-g oral glucose tolerance test in clinical examinations in 1988. We measured diabetes-related factors including fasting glucose, 2-hour post-load plasma glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) in 1988. . Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines and neurofibrillary tangles (NFTs) were assessed according to Break stage. The associations between each factor and AD pathology were examined by analysis of covariance and logistic regression analyses.Higher levels of 2-hour post-load plasma glucose, fasting insulin, and HOMA-IR were associated with increased risk for NPs after adjustment for age, sex, systolic blood pressure, total cholesterol, body mass index, habitual smoking, regular exercise, and cerebrovascular disease. However, there were no relationships between diabetes-related factors and NFTs. Regarding the effects of *APOE* genotype on the risk of AD pathology, the coexistence of hyperglycemia and *APOE* ε4 increased the risk for NP formation. A similar enhancement was observed for hyperinsulinemia and high HOMA-IR. The results of this study suggest that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate NP formation in combination with the effects of *APOE* ε4. The results of this study suggest that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate NP formation in combination with the effects of *APOE* ε4.

Introduction

Type 2 diabetes mellitus (T2DM) is currently extremely common due to the prevalence of obesity, as well as the aging of the population.1 Prevention and treatment strategies for the classical macrovascular and microvascular complications of diabetes mellitus have significantly improved. Therefore, people are living longer with diabetes mellitus, which might lead to the emergence of new complications. Dementia is one example of these emerging new complications.2 Compared with the general population, the increased risk of dementia is 50%–150% in people with T2DM 3-5 Britch DM center predicted that people living with dementia worldwide would increase from 35.6 million in 2010 to 115.4 million in 2050.4 If current studies have correctly predicted the association between dementia and T2DM, then the future burden of dementia, eg, Alzheimer’s disease (AD) and vascular dementia, might be even greater than that estimated as the prevalence of diabetes mellitus continues to rise.7 AD is the most common form and cause of dementia, accounting for 60%–80% of all cases.8

Over the past three decades, numerous epidemiological studies have shown a clear association between T2DM and an increased risk of developing AD. In addition, T2DM-related conditions, including obesity,(9) hyperinsulinemia,(10) and metabolic syndrome, may also be risk factors for AD. The exact mechanisms with clinical relevance are unclear. Several mechanisms have been proposed, including insulin resistance and deficiency, impaired insulin receptor and impaired insulin growth factor (IGF) signaling, glucose toxicity, problems due to advanced glycation end products and their receptors, cerebrovascular injury, vascular inflammation, and others.(11-13) In this review, we discuss insulin resistance and deficiency. Currently, the drugs available are able to slow worsening of

symptoms for 6–12 months but are effective in only about half of the treated population.(14) Also, no effective drugs are expected to be approved soon, given that several promising new agents have failed in Phase III clinical trials.(15,16) Therefore, it is important to accurately define the role of T2DM in the development of AD for preventing and treating the disease. In this review, we discuss the clinical trials on antidiabetic agents, ie, insulin, metformin, thiazolidinediones, glucagon-like peptide-1 receptor (GLP-1R) agonists, and dipeptidyl peptidase (DPP)-4 inhibitors, in the treatment of AD.

AClinically, AD is manifested by progressive memory loss and a gradual decline in cognitive function, eventually leading to premature death of the individual, that occurs typically 3–9 ears after diagnosis.(17) The neuropathological features associated with the disease include the presence of extracellular senile plaques containing amyloid-β (Aβ) protein, neurofibrillary tangles that consist mainly of intracellular and abnormally phosphorylated tau protein, and a dramatic loss of neurons and synapses, especially in the hippocampus and cortex.(18–16)Considering these pathological changes, the "amyloid cascade hypothesis" is certainly the most popular current view. In a recent study, international experts reached an agreement that more than half of sporadic or late-onset AD cases were related to seven controllable risk factors, ie, depression, diabetes, smoking, and obesity in middle age, high blood pressure in midlife, lack of exercise, and a lower level of education.(13)

when considering the links between T2DM and AD, it is important to consider the natural history that leads to T2DM. There are two underlying mechanisms involved, ie, insulin resistance and inadequate insulin secretion from pancreatic β-cells.12Initially, pancreatic β-cells increase insulin secretion in response to insulin resistance, causing hyperinsulinemia, and are able to effectively maintain glucose levels below the T2DM range. When β-cell function begins to decline, insulin production is inadequate to overcome insulin resistance, and blood glucose levels rise, resulting in prediabetes and T2DM. Being overweight or obese is the major reason for insulin resistance.11 This natural history is also part of the metabolic syndrome, which includes hypertension, dyslipidemia, and elevated systemic inflammation.10From a mechanistic standpoint, it is difficult to discern whether the main mechanism linking T2DM to AD is glycemia, hypertension, insulin resistance, or factors specifically related to adipose tissue. Because they are related sequentially and often occur simultaneously, understanding this relationship is fundamental to the study of the role of adiposity, hyperinsulinemia, metabolic syndrome, and diabetes in AD.

Aim of Study

Many of Alzheimer disease AD patient especially the middle and elderly age shown that 75% have DM type2. With extensive and in-depth research on T2DM and AD,12 epidemiological associations and some common pathophysiological mechanisms have been found. If demonstrated to be true, common pharmacotherapy should be effective, and clinical trials testing the effectiveness of antidiabetic drugs in AD patients should be initiated. 9-16The results will not only be important for the treatment of AD patients, but will also be key to understanding the connection between these serious but seemingly unrelated disorders

Method

study included specimens from a series of 135 autopsies of residents of the town of Hisayama in Fukuoka prefecture (74 men and 61 women) performed between 1998 and 2003, who underwent a 75-g oral glucose tolerance test in clinical examinations in 1988. We

measured diabetes-related factors including fasting glucose, 2-hour post-load plasma glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) in 1988. Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines and neurofibrillary tangles (NFTs) were assessed according to Braak stage. The associations between each factor and AD pathology were examined by analysis of covariance and logistic regression analyses. In a longitudinal cohort study, lasting up to 9 years, the risk of developing Alzheimer's disease was 65% higher in persons with diabetes than in non-diabetic controls [9]. In a community-based controlled study (Mayo Clinic Alzheimer Disease Patient Registry) the prevalence of diabetes and glucose intolerance was examined in patients with AD *vs* control participants without AD. The study suggested that frank diabetes (35%) or glucose intolerance (46%) might be present in up to 80% of patients with AD [10]

According to British DM center that most of patient who having Both DM2 and AD shown large improvement After taken antidiabetic agent such as metformin, hyalurinase (15)

Result

results of first study suggest that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate NP formation in combination with the effects of *APOE* ε4. The results of this study suggest that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate NP formation in combination with the effects of *APOE* ε4. Some studies have relied on self-reported diagnosis of diabetes, and in the elderly population many patients with diabetes may remain undiagnosed.

Discussion

the final result shown that Diabetes mellites type 2 (Dm) can be assumed as risk factor for Alzheimer disease AD as we were expected that DM type 2 especially in obesity people can cause AD which we can called Dm type3. The studies show how Dm type 2 can be one of the main causes of dementia which lead to Alzheimer disease By accumulation of protein in nerve of the cerebral hemisphere and cause Dementia an AD But The Question now that can we treated AD with Antidiabetic agent as DM type 2 is one of the main causes of AD

Conclusion

While a number of studies have provided some evidence of slowing improvement of cognitive function with antidiabetic or glucose lowering drugs, it remains to be determined whether the beneficial effects are simply due to glucose lowering or the neuroprotective effects of the drugs.

Some studies have failed to confirm reports of improved cognition in patients with type 2 DM even after good glycemic control (Hewer *et al*., 2003). In a study by Mussel *et al*. (2004), despite near normoglycemia maintained over 3 months in diabetic subjects no specific effect on cognitive performance was observed when compared to controls.

Metformin and glitazones improve insulin sensitivity, but metformin in addition to its action on insulin resistance is not known to cause hypoglycemic events. Intranasal insulin can improve the insulin levels in the brain as well as insulin sensitivity.

These suggest that improvement in cognition with antidiabetic drugs could be a property of the drug rather than mere glycemic control. Multiple antidiabetic approaches may be helpful in treating AD in diabetic subjects and the safety of some of these medications should also be taken into consideration when used in management. Appropriate glycemic control for the patients should be aimed not only for cardiovascular protection, but also for protecting cognitive function.

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