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β-Amyloid-induced cognitive dysfunction impairs glucose homeostasis by increasing insulin resistance and decreasing β-cell mass in non-diabetic and diabetic rats

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ABSTRACT

Objective. β-Amyloid accumulation in the brain may impair glucose homeostasis in both the brain and peripheral tissues. The present study investigated whether β-amyloid deposition in the hippocampus impairs glucose homeostasis by altering insulin sensitivity, glucose-stimulated insulin secretion or β-cell mass.

Methods. Male rats were divided into two groups: a non-diabetic sham group and a diabetic partial pancreatectomized (Px) group. Each group was then subdivided into three treatment groups that received intra-CA1 infusions of β-amyloid (25–35; AMY), β-amyloid (35–25; RAMY; non-plaque forming), or saline at a rate of 3.6 nmol/day for 14 days.

Results. After 4 weeks, cognitive function measured by passive avoidance and water maze tests was impaired in non-diabetic rats that received AMY compared with rats that received saline or RAMY. Furthermore, diabetes exacerbated cognitive dysfunction in AMY-infused rats. This was associated with the hyperphosphorylation of tau as a result of attenuated insulin signaling (pAkt→pGSK) through decreased phosphorylation of cAMP responding element binding protein in the hippocampus of non-diabetic and diabetic rats. AMY exacerbated whole-body and hepatic insulin resistance in non-diabetic and diabetic rats. However, AMY potentiated glucose-stimulated insulin secretion in non-diabetic and diabetic rats, but caused decreased β-cell mass via increased β-cell apoptosis and decreased β-cell proliferation. As a result, glucose homeostasis was maintained by potentiating insulin secretion in diabetic rats, but may not be sustainable with further decreases in β-cell mass.

Conclusion. Cognitive dysfunction attributable to β-amyloid accumulation in the hippocampus might be related to disturbed glucose homeostasis due to increased insulin resistance and decreased β-cell mass.

1. Introduction

Over the past century, life expectancy has increased markedly around the world. The increase in life expectancy, however, is associated with an increase in the prevalence of chronic diseases, including type 2 diabetes, hypertension, cardiovascular disease, and Alzheimer's disease [1]. The worldwide incidence of Alzheimer's disease was 26.6 million in 2006, and

Abbreviations: β-amyloid (25–35), AMY; β-amyloid (35–25), RAMY; partial pancreatectomy, Px; sham-operation, Sham; PKB or Akt, protein kinase B; CREB, cAMP responding element binding protein; GSK, glycogen synthase kinase; BrdU, 5-bromo-2-deoxyuridine; HOMA-IR, Homeostatic model assessment for insulin resistance.

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the prevalence is expected to quadruple to about 1.2% of the population by 2050 [2,3]. Given the increasing rates of dementia, including Alzheimer's disease, future studies should investigate the pathological etiology of such diseases.

The pathophysiology of Alzheimer's disease is currently unknown, but the prevailing hypothesis is that it involves an amyloid cascade [4]. Amyloid precursor protein is expressed in the brain, primarily in neurons, where it is metabolized into β-amyloid (1–40) and (1–42) peptides, which aggregate to form amyloid plaques characteristic of Alzheimer's disease [5,6]. Maesako and colleagues have shown that obesity induced by a high fat diet increases β-amyloid levels in the brain of amyloid precursor protein transgenic mice and that exercise effectively prevents the deposition of β-amyloid [7]. In addition, individuals with obesity have higher levels of amyloid precursor protein in their adipose tissue and higher blood concentrations of β-amyloid which are positively correlated with body fat [8]. Obesity is known to increase peripheral insulin resistance, as well as brain insulin resistance. Moreover, the impairment of insulin signaling in the parietotemporal and frontal areas has been shown to induce Alzheimer's disease [9]. Therefore, obesity increases the odds of developing Alzheimer's disease.

Alzheimer's disease is closely associated with type 2 diabetes and is sometimes referred to as "brain diabetes or type 3 diabetes" [10]. Older individuals with type 2 diabetes have a higher risk for vascular dementia and Alzheimer's disease-type dementia [11], although the mechanisms underlying diabetes-related cognitive dysfunction remain unknown. Hyperglycemia in type 2 diabetes may damage neurons in the brain through osmotic insults, oxidative stress, inflammation, and protein deformation with advanced glycated end-products [12]. Hyperinsulinemia in type 2 diabetes also accelerates the symptoms of Alzheimer's disease through β-amyloid aggregation in hippocampal neurons [12–14]. However, it is presently unclear how β-amyloid deposits in the brain affect glucose regulation in the brain and in other tissues and organs. The present study investigated glucose homeostasis in non-diabetic and diabetic rats with Alzheimer-type dementia induced by β-amyloid injection into the hippocampus. The experiments showed that both non-diabetic and diabetic rats with Alzheimer-type dementia, induced by hippocampal β-amyloid infusion, exhibited disturbances in glucose regulation.

2. Materials and methods

2.1. Animals and diets

Male Sprague Dawley rats, weighing 232 ± 16 g, were housed individually in stainless steel cages in a controlled environment (23 °C and a 12 hour light and dark cycle) with unrestricted access to diets and water. The diet was a semi-purified modified AIN-93 formulation [15] with energy sources being 48% carbohydrate, 22% protein, and 30% fats. The sources of carbohydrates, protein, and fats were starch and sucrose, casein, and lard, respectively. The diet composition was similar to a normal human diet. All surgical and experimental procedures were performed in accordance with the recommendations found in the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health, USA and they were approved by the Institutional Animal Care and Use Committee of Hoseo University, Korea.

2.2. Surgical procedures

One group of rats received a 90% pancreatectomy (Px) using the Hosokawa technique, and another group received a sham operation [16]. One week later, serum glucose levels were measured in the rats. Px rats with random-fed serum glucose levels less than 7 mM were excluded from the study. All Px rats included in the study had non-fasting serum glucose levels between 9.4 and 11.8 mM. After Px, the remaining pancreas was regenerated to about 50% of its original size and the insulin secretion capacity of the rats was lower than that of the sham rats by approximately 40–50%. The rats developed no symptoms associated with nutrient malabsorption or ketosis, and the ratio of α- to β-cells was similar to that in other type 2 diabetic animals [16–18]. Sham-operated (Sham) rats had random-fed serum glucose levels of 5.3–6.5 mM and showed no symptoms of diabetes.

After 3 days, the non-diabetic sham and diabetic Px rats were anesthetized with an intraperitoneal injection of a ketamine and xylazine mixture (100 mg and 10 mg/kg body weight, respectively) and placed in a stereotaxic device. A midline incision was made on the scalp, exposing the periosteum, and a stainless steel cannula was implanted to stereotaxically connect an osmotic pump for infusions into bilateral CA1 subregions using the following coordinates: lateral, −3.3 mm from the bregma; posterior, 2.0 mm from the midline; ventral, −2.5 mm from dura [5,17]. The cannula was secured with dental cement and connected to 22-gauge tubing filled with one of the following: saline, β-amyloid (25–35), which was named AMY, or β-amyloid (35–25), named RAMY. RAMY had the reverse sequence of AMY and thus did not accumulate in the brain, as confirmed by immunohistochemistry using β-amyloid antibody. The β-amyloid (25–35) and β-amyloid (35–25) was dissolved in sterile saline and stored at −20 °C before use.

2.3. Experimental design and metabolic analysis

The sham (non-diabetic) and Px (diabetic) rat groups were each subdivided into three treatment groups: Px-AMY, Px-RAMY, and Px-saline (Px-CON); and Sham-AMY, Sham-RAMY, and Sham-saline (Sham-CON). Twenty rats were used per treatment. Saline, AMY, and RAMY were administered into bilateral CA1 subregions via an osmotic pump (Alzet Osmotic Pump Company, Cupertino, CA) at the rate of 3.6 nmol/day for 14 days. Fig. 1 shows the experimental design. Overnight-fasted serum glucose levels, food and water intake, and body weight were measured at designated times every week. After completing the β-amyloid infusion, rats were maintained for 2 more weeks to assure that β-amyloid aggregation was sustained and to allow time for metabolic changes to develop due to β-amyloid accumulation.

2.4. Passive avoidance test

After 27 days post-β-amyloid infusion, the rats were tested for short-term memory deficits using a passive avoidance apparatus consisting of a two-compartment dark/light shuttle box [20].