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Renin-angiotensin system blockers affect cognitive decline and serum adipocytokines in Alzheimer's disease

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Abstract

Background: Accumulating evidence indicates an association of Alzheimer's disease (AD) with the metabolic syndrome (MetS), characterized by visceral fat accumulation with insulin resistance and altered secretion of adipocytokines such as adiponectin and leptin. The renin-angiotensin system (RAS) regulates blood pressure and insulin resistance. Recent studies suggest that the RAS plays crucial roles in cognitive functions and that adipocytokines exert neuroprotective activity in the brain. We investigated whether RAS blockers (RASB) affect adipocytokines and cognitive function in patients with AD.

Methods: We studied 78 patients with a diagnosis of probable AD according to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition and 106 nondemented control subjects who visited our clinic with a main complaint of headache or dizziness. We examined retrospectively the effects of RASB on adipocytokines and cognitive decline in patients with AD who were divided into three groups: hypertension treated with RASB (HT-RASB; n = 17), hypertension treated with other antihypertensive drugs (HT-other; n = 34), and no hypertension (non-HT; n = 27).

Results: The HT-RASB group had a significantly higher serum leptin level and a relatively larger visceral fat area than the other groups, because of the bias toward patients with MetS in this group. The HT-RASB group also had a significantly lower immunoreactive insulin level, a relatively low homeostasis model assessment as an index of insulin resistance, and a relatively high serum adiponectin level among the three groups. Cognitive decline, estimated on the basis of the mean annual decline using the Hasegawa Dementia Scale score was significantly low in the HT-RASB group.

Conclusion: Treatment with RASB might modulate serum adipocytokines and glucose homeostasis, potentially slowing cognitive decline in patients with AD.

Keywords: Renin-angiotensin system; RAS; Alzheimer's disease; Visceral fat; Adiponectin; Leptin

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting up to 50% of elderly persons 85 years or older, the fastest growing segment of the population [1]. The pathological hallmarks of AD are amyloid β peptide (Aβ) deposition [2], intracellular neurofibrillary tangles composed of abnormal phosphorylated tau protein, and cholinergic pathway deficits. Risk factors for AD can be classified as genetic and nongenetic. Recently, nongenetic risk factors for AD have received considerable attention as possible therapeutic targets and include vascular risk factors, such as hypertension, dyslipidemia, diabetes, hyperinsulinemia, and metabolic syndrome (MetS) [3–5]. The most common cause of MetS is the accumulation of visceral fat [6]. Adipose tissue secretes a variety of bioactive substances called adipocytokines, such as tumor necrosis factor-α and monocyte chemoattractant 1, which cause obesity-related morbidity and insulin resistance. Adipose tissue also secretes anti-inflammatory adipocytokines such as adiponectin, which protect against insulin resistance and atherosclerosis. Leptin, another adipocytokine, regulates

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body weight by modulating food intake and energy expenditure centrally [7]. Leptin also has a role in the action of insulin in target organs, as well as in the oxidation of free fatty acids in skeletal muscle [8]. Thus, adipocytokines are attractive therapeutic targets in obesity and related conditions.

Recently, several large clinical studies [9,10] have reported that antihypertensive drugs that modulate the renin-angiotensin system ([RAS]; i.e., RAS blockers [RASB], such as angiotensin receptor blockers [ARBs] or angiotensin-converting enzyme [ACE] inhibitors), are associated with a decreased incidence of AD and reduced rates of cognitive decline in patients with mild cognitive impairment [11]. The RAS is implicated in hypertension and adipose tissue metabolism [12] and has recently attracted interest because of its potential involvement in the pathogenesis of AD [11]. The RAS exerts its effects through the generation and action of angiotensin II, which has potent vasoconstrictor, antinatriuretic, and dipsogenic properties. Angiotensin II is generated by the serial cleavage of angiotensinogen, first by renin, and then by ACE. Angiotensin II exerts its well-known hypertensive effects by binding to its two receptors (AT_1R and AT_2R) [13]. A potential relation between ACE and AD was first suggested by human genetic studies, which reported that an insertion/deletion polymorphism within intron 16 of the *ACE* gene is associated with AD [14]. In addition to vascular systems, accumulating evidence suggests that the brain has certain components of the RAS that may have crucial roles in learning and memory processes [15,16]. For example, ACE is upregulated in the hippocampus, frontal cortex, and caudate nucleus of patients with AD [17,18]. In adipose tissues, angiotensin II participates in adipocyte growth, differentiation, and metabolism, thereby reducing adiponectin secretion [19]. Treatment with RASB thus substantially increases adiponectin levels and may improve insulin sensitivity in hypertensive patients [20]. Therefore, RASB has been recently recommended as the antihypertensive drug of choice for Japanese patients with MetS [21]. Because MetS is one of the nongenetic risk factors for AD, RASB also may affect cognitive function beneficially by improving insulin resistance. However, whether or how RASB affects secretion of adipocytokines and cognitive functions in patients with AD has yet to be studied. Therefore, we examined the effects of RASB on visceral fat depots, adipocytokines, immunoreactive insulin (IRI), and cognitive decline in patients with AD.

2. Methods

2.1. Subjects

We analyzed retrospectively Japanese patients with AD who presented at Nara Medical University Hospital between January 2005 and December 2006. Inclusion criteria in the AD group were as follows: (1) a diagnosis of probable AD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [22] and (2) informed consent to undergo brain magnetic resonance imaging (MRI), abdominal computed tomographic (CT) scanning, and the evaluation of cognitive functions by Mini-Mental State Examination (MMSE) and the revised version of Hasegawa's dementia scale (HDS-R). Exclusion criteria were as follows: (1) severe dementia (HDS-R score, <10 points or MMSE score, <10 points), (2) unstable status not permitting regular visits to our clinic, and (3) less than 1 year had elapsed since the first diagnosis of AD in our clinic. A total of 78 patients (30 men and 48 women; age, 76.4 $\pm$ 7.9 years; range, 52–90 years) met these conditions and were assigned to the AD group. The average length of follow-up was 2.45 $\pm$ 0.95 years (range, 1–4.33 years). As control subjects, we studied 106 nondemented subjects (39 men and 67 women; age, 76.6 $\pm$ 5.2 years; range, 66–90) who also presented within the same period with a main complaint of headache or dizziness, but who had no clinical evidence of ataxia, parkinsonism, autonomic failure, or hypertension.

All patients with AD were receiving donepezil hydrochloride. We confirmed whether the patients were receiving specific RASB; if so, the duration of treatment was estimated on the basis of their medical records. The patients were divided into three groups: those who had hypertension treated with RASB (HT-RASB; n = 17), those who had hypertension treated with other antihypertensive drugs (HT-other; n = 34), and those who had no hypertension (non-HT; n = 27). All patients in the HT-RASB group had received RASB for at least 1 year (32.7 $\pm$ 11.6 months), and patients in the HT-other group had received other antihypertensive drugs for 30.6 $\pm$ 10.6 months.

2.2. Anthropometry

Anthropometric measurements (height, weight, and waist circumference [WC]) were acquired with the participant in a standing position. Body mass index (BMI) was calculated as weight/$(\text{height})^2$, where weight was measured in kilograms and height was measured in centimeters. WC at the umbilical level was measured in the late exhalation phase while standing, as reported previously [23]. Blood pressure was measured in the sitting position.

2.3. Laboratory measurements

Blood was withdrawn after a 5-hour fast. Routine hematochemical analyses, including fasting blood sugar (FBS), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were carried out using standardized methods. IRI, leptin, and adiponectin were measured by enzyme-linked immunosorbent assay at SRL, Inc. (Tokyo, Japan). Homeostasis model assessment as an index of insulin resistance (HOMA-IR) was calculated by following formula: IRI $\times$ FBS/405, where IRI was measured in microunits per milliliter and FBS was measured in milligrams per deciliter.