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Original Research Article

Rivastigmine Improves Appetite by Increasing the Plasma Acyl/Des-Acyl Ghrelin Ratio and Cortisol in Alzheimer Disease

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Keywords
Rivastigmine · Appetite · Alzheimer disease · Ghrelin · Acyl/des-acyl ghrelin ratio · Cortisol · High-density lipoprotein cholesterol

Abstract
Background: Weight loss accelerates cognitive decline and increases mortality in patients with dementia. While acetylcholinesterase (AChE) inhibitors are known to cause appetite loss, we sometimes encounter patients in whom switching from donepezil (AChE inhibitor) to rivastigmine (AChE and butyrylcholinesterase [BuChE] inhibitor) improves appetite. Since BuChE inactivates ghrelin, a potent orexigenic hormone, we speculated that rivastigmine improves appetite by inhibiting BuChE-mediated ghrelin inactivation. ***Methods:*** The subjects were patients with mild to moderate Alzheimer disease treated with either rivastigmine patch (n = 11) or donepezil (n = 11) for 6 months. Before and after treatment, we evaluated appetite (0, decreased; 1, slightly decreased; 2, normal; 3, slightly increased; 4, increased), cognitive function, and blood biochemical variables, including various hormones. ***Results:*** Rivastigmine treatment significantly improved appetite (from 1.6 ± 0.5 to 2.6 ± 0.7), whereas donepezil treatment did not (from 2.0 ± 0.0 to 1.8 ± 0.4). Simultaneously, rivastigmine, but not donepezil, significantly decreased the serum cholinesterase activity (from 304.3 ± 60.5 to 246.8 ± 78.5 IU/L) and increased the cortisol level (from 11.86 ± 3.12 to 14.61 ± 3.29 μg/dL) and the acyl/des-acyl ghrelin ratio (from 4.03 ± 2.96 to 5.28 ± 2.72). The levels of leptin, insulin, total ghrelin, and cognitive function were not significantly affected by either treatment. ***Conclusions:*** Our results suggest that compared with donepezil, rivastigmine has the advantage of improving appetite by increasing the acyl/des-acyl ghrelin ratio and cortisol level, thereby preventing weight loss.

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Introduction

Alzheimer disease (AD) is the most common form of dementia, affecting about 50% of elderly persons >85 years old [1]. The pathological hallmarks of AD are amyloid β peptide (Aβ) deposition [2] and intracellular neurofibrillary tangles composed of abnormal phosphorylated tau protein. These pathological changes are thought to initiate cholinergic and other neuronal deficits. Epidemiological studies have shown that vascular risk factors such as hypertension, diabetes, dyslipidemia, metabolic syndrome, overweight, and obesity during middle age are also risks of AD in later life [3–5].

Meanwhile, there is also the so-called "obesity paradox": In elderly people near the age of onset of dementia, low body weight is rather a risk factor for the development of dementia. For example, a longitudinal study performed by the University of Washington [6] and the Honolulu-Asia Aging Study from Oahu, Hawaii [7] showed that weight loss precedes disease onset in patients with AD. Cerebral accumulation of Aβ in patients with mild cognitive impairment has been shown to be negatively correlated with body weight [8]. Pathological findings of dementia in autopsy studies were negatively correlated with body mass index (BMI) in normal elderly individuals [9]. Furthermore, an amyloid imaging study using Pittsburgh compound B has shown that lower BMI is associated with greater cortical amyloid burden during the preclinical stage of AD [10].

Cognitive decline has been reported to be accelerated by weight loss in patients with AD. In a 4-year follow-up study of 414 patients with AD residing in France, patients whose body weight decreased by >4% in the first year showed more rapid decrease in Mini-Mental State Examination (MMSE) score than the other patients [11]. Thus, weight loss causes a "malignant cycle" resembling "the cycle of frailty" [12], which accelerates the onset and progression of dementia and affects life prognosis. Kai et al. [13] reported that about 80% of patients with AD showed some eating disturbance, whereas only 20% of normal elderly people did so. Anorexia can occur at any stages in patients with AD and cause weight loss [13] and lead to the "malignant cycle." Thus, improvement of nutritional status and prevention of weight loss is an important issue for patients with AD.

The cholinesterase inhibitor (ChEI) donepezil, the first-line therapeutic agent for AD, often causes gastrointestinal adverse reactions, decreasing appetite and leading to weight loss [14]. On the other hand, we sometimes encounter patients in whom switching from donepezil to rivastigmine improves appetite. We speculate that the underlying reason for this improvement is twofold: first, donepezil is an oral drug and can easily act on the gastrointestinal tract, whereas rivastigmine is a percutaneously administered patch and thus may not directly act on this organ system; second, unlike other ChEIs, rivastigmine has inhibitory effects on not only acetylcholinesterase (AChE), but also on butyrylcholinesterase (BuChE) [15]. BuChE is known to inactivate ghrelin, a potent orexigenic hormone secreted from the stomach in the hunger state to increase appetite and promote food intake [16].

Ghrelin, consisting of 28 amino acids, shows a unique structure in its active form, which has an N-octanoyl modification of serine at position 3. This modification is essential for its interaction with receptors on the pituitary gland to potentiate the secretion of growth hormone and on the hypothalamus to stimulate appetite. Acyl ghrelin (active form) is dehydrolyzed by proteases such as BuChE into an inactive form, des-acyl ghrelin, which is the major form in the circulation [15]. Since rivastigmine inhibits BuChE, we speculated that rivastigmine improves appetite by inhibiting BuChE-mediated ghrelin inactivation. To test this hypothesis, we administered donepezil and rivastigmine to patients with AD for 6 months and evaluated their effects on appetite and various hormones, including acyl and des-acyl ghrelin, insulin, leptin, and cortisol, all of which are associated with appetite.

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Methods

Subjects

The subjects were 22 outpatients with mild to moderate AD who visited our clinic from January to September 2013. The criteria for inclusion into the AD group were as follows: (i) probable AD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [17] and (ii) provision of informed consent to undergo brain magnetic resonance imaging and evaluation of cognitive functions by the MMSE and the Revised Hasegawa Dementia Scale (HDS-R). Exclusion criteria were as follows: (i) severe dementia (HDS-R score <10 and/or MMSE score <10 and abasic status with or without a walking aid), (ii) unstable status not permitting regular visits to our clinic, and (iii) patients receiving memantine, as some clinical and animal studies have shown that memantine has appetite-suppressing effects [18, 19]. The participants (MMSE score 18.0 ± 5.9 points, 9 men, 13 women, average age 78.4 years) were divided into two groups and treated with either rivastigmine patch (n = 11) or donepezil (n = 11) for 6 months. Six patients in the rivastigmine group were given ChEIs for the first time; the other 5 patients had previously received donepezil, but were switched to rivastigmine patch in this study because they complained of appetite loss. Before and after the treatment, anthropometry, blood examination, appetite evaluation, and cognitive function tests were performed.

Anthropometry

Anthropometric measurements (height, weight, and waist circumference) were performed in a standing position. BMI was calculated as weight in kg divided by height in cm^2. Waist circumference at the umbilical level was measured in the late exhalation phase with the subject standing. We defined the metabolic syndrome according to guidelines for the diagnosis of the metabolic syndrome in Japan [20].

Laboratory Measurements

Blood samples were taken at about 8:30 a.m. before breakfast. Routine hematochemical analyses, including fasting blood sugar, triglycerides, high-density lipoprotein cholesterol (HDL-C), and cholinesterase, were carried out using standardized methods. Cortisol was measured by radioimmunoassay, and immunoreactive insulin and leptin were measured by enzyme-linked immunosorbent assay (ELISA) at SRL Inc. (Tokyo, Japan) on a commercial basis. Acyl ghrelin and des-acyl ghrelin were measured using the Mitsubishi Chemical Medience Corporation ELISA kit. Blood samples for measurement of acyl ghrelin and des-acyl ghrelin were collected into tubes containing EDTA and a protease inhibitor and were treated with 100 μL of 1 N HCl per mL of collected plasma to prevent the degradation of acyl ghrelin.

Appetite Score

When patients visited the hospital, physicians asked them and their caregivers about their appetite and classified patients' appetite into five degrees (0, decreased; 1, slightly decreased; 2, normal; 3, slightly increased; 4, increased) by referring to the Functional Assessment of Cancer Therapy scale [21].

Cognitive Functions

Cognitive functions were estimated on the basis of the scores on MMSE and HDS-R, a scale widely used to evaluate dementia in Japan and other East Asian countries [22].

Table 1. Baseline characteristics of subjects in the rivastigmine and donepezil groups

	Rivastigmine (n = 11)	Donepezil (n = 11)
Age, years	77.3±7.8	79.6±7.2
Women	5	8
Cognitive function		
MMSE score (of 30 points)	16.1±7.3	19.9±4.1
HDS-R score (of 30 points)	14.5±7.5	19.1±4.1
Anthropometry		
Body weight, kg	48.5±9.2	52.8±10.1
Waist circumference, cm	82.4±9.5	83.4±8.2
Body mass index	21.30±3.98	22.49±2.67
Metabolic syndrome	0	0
Hypertension	7	6
Hyperglycemia	2	3
Dyslipidemia	1	3
Abdominal obesity	0	1
Number of risk factors	1.0±0.9	1.1±0.9
Average daily dose of ChEI, mg	9.75±1.75	5.50±2.24

Data are presented as n or mean ± standard deviation. We defined the metabolic syndrome according to guidelines for the diagnosis of metabolic syndrome in Japan [20]. ChEI, cholinesterase inhibitor; HDS-R, Revised Hasegawa Dementia Scale; MMSE, Mini-Mental State Examination.

Statistical Analysis

The demographic and clinical characteristics of subjects in the rivastigmine group and the donepezil group were compared using the Students t test for continuous measures and the χ^2 test for categorical measures (Tables 1, 2). A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of the SPSS software, version 17.0.

Results

The patients' baseline characteristics are shown in Table 1. There were no significant differences in age, cognition, body weight, or background illness between the rivastigmine group and the donepezil group. The average daily doses of rivastigmine patch and donepezil were 9.75 ± 1.75 mg and 5.50 ± 2.24 mg, respectively.

Table 2 shows the cognition, body weight, and biochemical markers in the blood before and after treatment with ChEIs for 6 months. Rivastigmine, but not donepezil, significantly decreased serum levels of cholinesterase ($p < 0.05$), which closely reflect peripheral BuChE activities [23]. Simultaneously, the acyl/des-acyl ghrelin ratio was significantly increased by rivastigmine ($p < 0.05$), associated with a slight, but not significant increase in both acyl and des-acyl ghrelin. In contrast, donepezil tended to decrease the acyl/des-acyl ghrelin ratio and the plasma levels of acyl and des-acyl ghrelin. Plasma cortisol and serum HDL-C levels significantly increased in the rivastigmine-treated group ($p < 0.05$). Notably, appetite scores were significantly increased by rivastigmine treatment ($p < 0.01$), but not by donepezil, which seems to support our hypothesis that rivastigmine improves appetite by inhibiting BuChE-mediated ghrelin inactivation. Body weight and waist circumference increased slightly in the rivastigmine group and decreased slightly in the donepezil group. Serum triglycerides, plasma leptin, and insulin levels were not altered significantly by either treatment. The results of the

Table 2. Comparison of patients treated with the cholinesterase inhibitors rivastigmine or donepezil

	Rivastigmine		Donepezil	
	pre	post	pre	post
MMSE score (of 30 points)	16.1±7.3	17.1±7.3	19.9±4.1	20.1±4.2
HDS-R score (of 30 points)	14.5±7.5	13.2±7.5	19.1±4.1	17.8±6.0
Body weight, kg	48.5±9.2	50.2±8.2	52.8±10.1	50.9±9.5
Waist circumference, cm	82.4±9.5	84.4±8.2	83.4±8.2	83.3±7.3
Body mass index	21.30±3.98	22.00±3.25	22.49±2.67	21.79±2.84
Appetite score (of 4 points)	1.6±0.5	2.6±0.7**	2.0±0.0	1.8±0.4
Triglycerides, mg/dL	109.2±44.7	95.4±43.0	120.2±57.1	104.2±35.5
HDL-C, mg/dL	63.3±17.3	68.4±15.0*	65.4±14.6	65.5±15.1
Cholinesterase, IU/L	304.3±60.5	256.8±78.5*	293.5±42.9	296.6±42.5
Fasting blood sugar, mg/dL	106.8±20.6	102.9±19.6	115.2±50.3	113.9±52.5
Immunoreactive insulin, mg/mL	5.47±2.08	4.49±2.40	6.56±1.96	6.79±3.01
Cortisol, μg/dL	11.86±3.12	14.61±3.29*	13.36±4.17	13.58±5.42
Leptin, ng/mL	6.25±5.66	7.90±7.33	5.00±1.73	5.30±2.52
Acyl ghrelin, fmol/L	14.60±13.51	18.29±11.49	17.21±15.62	9.11±5.78
Des-acyl ghrelin, fmol/L	367.67±259.5	374.41±249.40	370.01±166.34	239.76±211.81
Acyl/des-acyl ghrelin ratio	4.03±2.96	5.28±2.72*	4.93±3.27	4.23±1.30

Data are presented as mean ± standard deviation. HDL-C, high-density lipoprotein cholesterol; HDS-R, Revised Hasegawa Dementia Scale; MMSE, Mini-Mental State Examination. * $p < 0.05$, ** $p < 0.01$.

cognitive function test indicated that there was no significant change in cognition in either the rivastigmine group or donepezil group. Cognitive function appeared to be maintained by these ChEIs for 6 months.

Discussion

The present study is an open-label, nonrandomized study. In choosing ChEIs (AChE or BuChE inhibitor), we determined it according to the benefit to patients. For example, we chose a patch for patients who wanted to avoid adverse effects such as gastrointestinal symptoms or patients taking a lot of oral internal medications. Actually, the rivastigmine group included 5 patients who had decreased appetite after administration of donepezil and changed to a patch. Therefore, there is a possibility that the rivastigmine group was biased toward lower appetite as compared with the donepezil group. Nonetheless, the appetite score significantly increased after 6 months of rivastigmine patch treatment. Various factors are involved in appetite control. Ghrelin is a neuroendocrine peptide involved in dietary intake and regulation of energy homeostasis, acting together with neurotensin and leptin. Acyl ghrelin is inactivated by proteases such as BuChE into des-acyl ghrelin. It is thought that the BuChE-inhibitory action of rivastigmine prevents the inactivation of ghrelin, leading to an increase in the appetite score. However, our results indicated that rivastigmine treatment did not induce a significant increase in acyl ghrelin or a significant decrease in des-acyl ghrelin. Several reasons may account for these findings. First, deoctanoylation of ghrelin is also mediated by various esterases in the blood. The activities of these esterases cannot be suppressed by rivastigmine and may inactivate ghrelin during and after blood sampling. Second, octanoylation of ghrelin occurs readily in the bloodstream as well as during subsequently storage of blood samples at room temperature despite the addition of EDTA and HCl.

These factors might have influenced the measurement of acyl and des-acyl ghrelin levels in collected blood samples. Nevertheless, the acyl/des-acyl ghrelin ratio in the samples remained significantly increased after rivastigmine treatment.

The plasma cortisol level was significantly increased by rivastigmine, but not by donepezil. Cortisol plays an important role in energy regulation and increases available energy through gluconeogenesis and lipolysis. Cortisol is a potent appetite stimulant and is used clinically to enhance the appetite of patients with terminal cancer [24]. Blood concentrations of cortisol increase during pregnancy, which contributes to body weight gain. The mechanism underlying rivastigmine-induced increase in cortisol is unclear. It has been shown that physostigmine, which also exerts inhibitory activity to both AChE and BuChE but not donepezil, increased the cortisol level in the blood of patients with AD [25], suggesting that physostigmine- and rivastigmine-induced increases in cortisol are most likely related to their BuChE-inhibitory activity.

Serum HDL-C significantly increased in the rivastigmine group, but not in the donepezil group. Since serum BuChE levels strictly correlate with the classical indicators of nutritional status such as albumin, lymphocyte count, cholesterol, and transferrin [26], BuChE may play a role in lipid metabolism. Several investigators have found significant relationships between cholinesterase activity and triglyceride, HDL-C, and low-density lipoprotein cholesterol (LDL-C) [27–30]. A previous study reported that BuChE knockout mice had 1.5-fold higher levels of plasma ghrelin than wild-type mice as well as high levels of total cholesterol, LDL-C, and very-low-density lipoprotein, and showed that these alterations were improved by introducing the *BuChE* gene using an adenovirus vector [31]. Although serum HDL-C levels in the mice were not reported, these findings suggest that BuChE affects not only plasma ghrelin, but also cholesterol levels and that rivastigmine increases HDL-C by inhibiting this enzyme.

While rivastigmine significantly increased the patients' appetite score, their body weight and waist circumference did not change significantly. Since elderly people are often affected by sarcopenia, it would be more informative for evaluation of rivastigmine to precisely examine body composition rather than body weight and abdominal circumference.

In conclusion, our results indicate that rivastigmine improves patients' appetite by increasing the active ghrelin ratio and the cortisol level in blood, which might contribute to halting the progression of dementia. Recent studies have shown that Aβ fibril deposition and conserved glucose metabolism in the brain of AD mouse models were attenuated by knocking out *BuChE* [32, 33]. Taken together, available evidence indicates that rivastigmine might be a useful therapeutic agent for preventing the development of dementia in patients with mild cognitive impairment and normal subjects. An important limitation of the present study is that the study group was small. Further investigations of larger numbers of subjects are necessary.

Statement of Ethics

This study was approved by the ethics committee of Nara Medical University and performed with due regard for the protection of privacy.

Disclosure Statement

None of the authors has any conflict of interest.

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