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Relationship between hypothalamic–pituitary–adrenal axis dysregulation and insulin resistance in elderly patients with depression

Katsutoshi Yokoyama [a,*], Takeshi Yamada [b], Hideaki Mitani [a], Sayaka Yamada [a], Shenghong Pu [a], Takehiko Yamanashi [a], Hiroshi Matsumura [a], Kazuyuki Nakagome [c], Koichi Kaneko [a]

[a] Division of Neuropsychiatry, Department of Brain and Neuroscience, Tottori University, Faculty of Medicine, 36-1 Nishi-cho, Yonago, Japan
[b] Division of Psychiatry, Kurayoshi Hospital, 43 Yamane, Kurayoshi, Japan
[c] National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo, Japan

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ABSTRACT

Cortisol dysregulation has been proposed to be involved in depression. Hypothalamic–pituitary–adrenal (HPA) axis dysregulation associated with major depressive disorder (MDD) was previously reported to be higher in the elderly. Furthermore, insulin resistance and the prevalence of type 2 diabetes are known to increase with aging. The aim of the present study was to determine whether a relationship existed between plasma cortisol levels following the dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test and insulin resistance evaluated by the homeostasis model assessment of insulin resistance (HOMA-R) in elderly MDD subjects. Fifteen unmedicated MDD inpatients and 17 age- and sex-matched healthy controls participated in this study. After overnight fasting, blood samples were collected to measure plasma glucose and insulin concentrations, estimate HOMA-R, and perform the DEX/CRH test to evaluate HPA axis function. The value of the area under the time curve of plasma cortisol concentrations ($Cort_{AUC}$) and peak cortisol values ($Cort_{peak}$) following the administration of DEX/CRH both correlated with HOMA-R in MDD group. In contrast, neither $Cort_{AUC}$ nor $Cort_{peak}$ correlated with HOMA-R in controls. This is the first study to directly demonstrate the relationship between HPA axis dysregulation assessed with the DEX/CRH test and the index of insulin resistance estimated as HOMA-R in elderly MDD patients.

1. Introduction

A relationship has been identified between MDD and type 2 diabetes, which have also been proposed to partially share a common etiology (Iwata et al., 2013); MDD was shown to increase the incidence of type 2 diabetes (relative hazard [RH] 1.63, 95% CI 1.31–2.02) (Golden et al., 2004) and the comorbidity rate of MDD in type 2 diabetic patients was estimated to be higher than that in the non-diabetic population (Gavard et al., 1993). A meta-analysis performed by Gavard et al. (1993) revealed that the prevalence of depression in current diabetic patients ranged between 8.5% and 27.3% (mean = 14.0%), which was three-fold higher than the prevalence of MDD in the general adult population.

The risk factors for MDD in diabetic patients include the burden of diabetes management and arteriosclerosis (Schillerstrom et al., 2008). On the other hand, the risk factors for diabetes in patients with depression involve reduced daily activities, overeating, and hypercortisolemia (Pariante and Lightman, 2008). Hypercortisolemia has been attributed to hypothalamic–pituitary–adrenal (HPA) axis dysregulation, which is one of the most reliable biological findings of MDD (Pariante and Lightman, 2008), has been implicated in the development of insulin resistance (Manoudi et al., 2012), and is a risk factor for type 2 diabetes (Brown et al., 2004). However, evidence for the relationship between hypercortisolemia and insulin resistance is limited to a cross-sectional study that only recruited normal volunteers (Rizza et al., 1982). This study demonstrated that cortisol-induced insulin resistance was caused by a decrease in both hepatic and extrahepatic sensitivity to insulin.

HPA axis dysregulation associated with MDD was previously shown to be more prevalent in the elderly (Hatzinger et al., 2011), and insulin resistance and the prevalence of type 2 diabetes have both been reported to increase with aging (Rowe et al., 1983). Regarding depression, community-based studies identified a relationship between aging

* Corresponding author. Tel.: +81 85938 6547; fax: +81 85938 6549.
E-mail address: kyinyonago@yahoo.co.jp (K. Yokoyama).

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and prevalence of MDD (Beekman et al., 1999; Naismith et al., 2012). Moreover, a meta-analysis revealed that aging itself may be an important risk factor for MDD (Snowdon, 2001). A previous study also found that the prevalence of type 2 diabetes was the highest in the elderly (Danaei et al., 2011). Taken together, these findings suggested that a positive relationship exists between hypercortisolemia arising from HPA axis dysregulation and insulin resistance in elderly MDD patients.

Elevated cortisol levels have been shown to worsen glucose tolerance (Di Dalmazi et al., 2012). Insulin resistance may aggravate type 2 diabetes and cardiovascular disease, but not hypercortisolemia, which may develop due to the excess secretion of adrenocorticotrophic hormone (ACTH) or administration of a glucocorticoid treatment, but not directly from insulin resistance (Meigs, 2003; Prague et al., 2013). Therefore, we hypothesized that depression or depressive episodes may have effects on cortisol dysregulation and also that the resultant hypercortisolemia may subsequently lead to the development of insulin resistance in patients with depression. In the present study, we investigated whether hypercortisolemia resulting from HPA axis dysregulation was directly associated with insulin resistance in elderly MDD patients. The primary aim of the present study was to determine whether plasma cortisol levels following the dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test correlated with insulin resistance evaluated with HOMA-R in elderly MDD subjects.

2. Methods

2.1. Subjects

Fifteen unmedicated inpatients from the psychiatry ward, Tottori University Hospital, Yonago, Japan and 17 age- and sex-matched controls participated in this study with written informed consent between November 2008 and December 2012 following a full explanation of the study. All were older than 60 years. Fifteen inpatients met the criteria of MDD from the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV). The diagnosis of MDD was then confirmed by Mini-International Neuropsychiatric Interview Control (M.I.N.I) (Sheehan et al., 1998). Seventeen control subjects were recruited from the community in Tottori, Japan via an official employment agency. They met neither current nor lifetime axis I disorders of DSM-IV, which was then confirmed by M.I.N.I. Exclusion criteria for all subjects were as follows; (1) somatic disorders such as diabetes, chronic inflammatory disease, autoimmune disease, endocrine disease, and neoplasm, which directly or the treatment of which could influence insulin resistance or plasma cortisol levels; (2) clinical evidence of other central nervous system disorders based on a clinical history and medical examination. Mental ability was examined using the Mini-Mental State Examination (Folstein et al., 1975) with a cut-off point of 24; (3) a current or past history of the abuse of illegal drugs or other substances such as benzodiazepines and alcohol; (4) past history of a head injury; and (5) taking any psychotropic drug such as antipsychotics, antidepressants, and mood stabilizers for the preceding two weeks prior to this study because these drugs are known to influence the HPA axis and insulin resistance (Bergman and Ader, 2005; Bschor et al., 2011; Kunzel et al., 2003; Mondelli et al., 2010).

This study was approved by the Ethics Committee of Tottori University Faculty of Medicine and all subjects gave written informed consent after a full explanation of the study.

2.2. Physical measurements and depression scale assessment

The heights (m) and weights (kg) of elderly MDD subjects were measured on admission, and just before this study for the control subjects. The Hamilton depression scale (HAM-D17) (Hamilton, 1960) was assessed in elderly MDD subjects.

2.3. Assessment of HPA function

The DEX/CRH test is the most sensitive measurement of HPA axis regulation (Kunugi et al., 2012), and was, thus, conducted to assess HPA axis regulation in all subjects. The test was performed with a PO pretreatment of 1.5 mg DEX ('decadron' 0.5 mg, Nichiiko Pharmaceutical Corporation, Toyama, Japan) at 23:00 h. An IV catheter with heparinized physiological saline was inserted into a forearm vein at 14:30 h on the following day, and 100 μg human CRH (hCRH 'TANABE', Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was injected through the catheter at 15:00 h immediately after the first (= 0 min) blood sampling. Blood samples were taken 30, 60, and 90 min after the injection of CRH in order to measure plasma ACTH and cortisol concentrations. Subjects rested supine in hospital beds throughout the test. Blood samples were cooled in ice water, rapidly centrifuged in a tube for 10 min at 3000 rpm at 4 °C, and then stored at −20 °C until later analyses. Plasma ACTH and cortisol concentrations were measured using an electrochemiluminescent immunoassay and chemiluminescent enzyme immunoassay, respectively, at SRL Co. (Tokyo, Japan). The limits of detection for ACTH and cortisol were 5.0 pg/ml and 1.0 μg/dl, respectively. $ACTH_{base}$ and $Cort_{base}$ were defined as the plasma concentrations of ACTH and cortisol, respectively, in the blood sample obtained at 15:00 h. $ACTH_{30}$, $ACTH_{60}$, and $ACTH_{90}$ were defined as the plasma ACTH concentrations measured 30, 60, and 90 min, respectively, after the IV infusion of CRH. $Cort_{30}$, $Cort_{60}$, and $Cort_{90}$ were similarly designated for plasma cortisol concentrations. The area under the time curve (AUC) was calculated according to the trapezoidal rule (e.g. $Cort_{AUC}$ for the AUC of cortisol). $Cort_{peak}$ was the peak value of the plasma cortisol concentration in response to CRH. $ACTH_{AUC}$ and $ACTH_{peak}$ were defined in a similar manner. Regarding criteria for the suppression of cortisol levels with DEX, we followed those described in a previous study (Kunugi et al., 2012), in which abnormal "non-suppression" was defined as $Cort_{base}$ of ≥ 5.0 μg/dl irrespective of the size of $Cort_{peak}$, and "intermediate-suppression" as $Cort_{base}$ of < 5.0 μg/dl and $Cort_{peak}$ of ≥ 5.0 μg/dl.

2.4. Assessment of insulin resistance

In the present study, insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-R) because it is one of the most extensively used measurements of insulin resistance in clinical settings (Wallace et al., 2004). Its formula is the basal insulin level multiplied by the basal plasma glucose concentration divided by 22.5. Normal values were previously estimated as 1.62 ± 0.96 (Matthews et al., 1985). After overnight fasting, blood samples were collected to determine plasma glucose and insulin concentrations. Plasma glucose levels were measured using an enzymatic assay and plasma insulin levels were measured using a chemiluminescent immune assay at SRL Co.

2.5. Schedule of the hormonal examination

Blood samples were collected on the first day. The PO pretreatment with 1.5 mg DEX was conducted on the second day at 23:00 h, and the DEX/CRH test was conducted on the third day.

2.6. Statistical analysis

In order to make comparisons between patient and control groups, an unpaired *t*-test was used to assess differences in the following items; age, BMI, and fasting blood sugar (FBS). The Mann–Whitney test was used to assess differences in the following items; $Cort_{peak}$, $ACTH_{peak}$, $Cort_{AUC}$, $ACTH_{AUC}$, and HOMA-R. Fisher's exact test was used to assess differences in the ratio of sex, non-suppression, and intermediate-suppression between the two groups. Spearman rank correlation coefficients were determined to assess the relationships among age, BMI, HAMD, and hormonal parameters, such as ACTH, cortisol, and HOMA-R because of the strongly skewed distribution of these hormonal parameters. A value of $p < 0.05$ was considered significant. Data analyses were performed using SSPS for Windows 17.0 (SSPA Inc. Chicago).

3. Results

The demographic and clinical characteristics of the elderly MDD patients and control subjects are shown in Table 1. No significant differences were observed in these characteristics or FBS, $Cort_{peak}$, $Cort_{AUC}$, $ACTH_{peak}$, $ACTH_{AUC}$, and HOMA-R between the two groups (Table 2). The ratio of the number of participants assessed as abnormal, non-, and intermediate-suppression in the DEX/CRH test was significantly higher in the patient group than in the control group (Fisher's exact test; $p < 0.05$, φ coefficient 0.39) (Table 3).

Metabolic characteristics, endocrinal responses, age, and HAMD for the elderly MDD subjects, controls, and all subjects are shown in Table 4. No correlation was observed between BMI and endocrinal parameters in all subjects, in the control subjects, and in the elderly MDD patients, with the exception of a correlation between BMI and HOMA-R in all subjects (Rho = 0.48; $p < 0.05$) and in the control subjects (Rho = 0.76; $p < 0.05$). However, this correlation was not found in the elderly MDD patients. Regarding the relationship