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Circulating obestatin is increased in patients with cardiorenal syndrome and positively correlated with vasopressin

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ABSTRACT

Obestatin regulates fluid and electrolyte homeostasis mainly by opposing the action of vasopressin (AVP). We measured plasma concentration of obestatin and AVP in patients with cardiorenal syndrome (CRS). Plasma AVP and obestatin concentration were measured in 34 patients with type II CRS. The data were compared to that in 31 patients with chronic kidney disease (CKD), 41 patients with chronic heart failure (CHF) and 30 healthy subjects. Obestatin was significantly higher in the patients with CRS (355.8 ± 85.1 pg/ml) than that in the healthy controls (212.3 ± 37.9 pg/ml, $P < 0.01$), the patients with CKD (246.7 ± 34.3 pg/ml, $P < 0.01$) and the patients with CHF (258.4 ± 112.1 pg/ml, $P < 0.01$). AVP was also significantly higher in the patients with CRS (65.1 ± 36.0 pg/ml) than that in the healthy controls (38.5 ± 20.1 pg/ml, $P < 0.01$), the patients with CKD (50.4 ± 24.8 pg/ml, $P < 0.01$) and the patients with CHF (54.6 ± 16.3 pg/ml, $P < 0.01$). Plasma concentration of obestatin was positively correlated with AVP plasma concentration in the overall analysis that included subjects from all disease categories ($r = 0.219$, $P < 0.05$), but not within the CRS group. Plasma obestatin and vasopressin were elevated in patients with CRS. Plasma obestatin concentration seemed to be positively correlated with plasma AVP.

1. Introduction

Heart failure is increasingly co-morbid with kidney failure. McClellan et al. [5] reported elevated serum creatinine (SCR) in 38% of the patients admitted to the hospital for heart failure. The concept of cardiorenal syndrome (CRS), however, has only recently attracted widespread attention. CRS was first officially defined at a consensus conference of the acute dialysis quality initiative in 2009 [8].

Sodium and water retention caused by heart failure is exaggerated by a decrease in the glomerular filtration rate [13]. Arginine vasopressin (AVP) increases body-fluid volume upon needs [11], and promotes CRS progression by fluid retention [7].

Obestatin is a 23 amino acid ghrelin gene-derived peptide hormone [17]. It is mainly produced in the stomach and other organs in the gastrointestinal tract. Obestatin has a variety of functions [12]. Samson et al. [9] reported that obestatin may act in the brain to inhibit water drinking. Obestatin inhibits dehydration-induced vasopressin secretion [10].

In the current study, we measured plasma concentration of obestatin and AVP in 34 patients with type II CRS [8]. The results were compared to that in patients with chronic heart disease (CHF) or chronic kidney disease (CKD) alone, and healthy controls. The potential relation between obestatin and AVP was also examined.

2. Subjects and methods

2.1. Subjects

This study enrolled 34 patients with CRS, 41 patients with CHF, 31 patients with CKD, and 30 healthy subjects. The patients with CRS, CHF, or CKD were recruited from those who were admitted to our hospital for work-up and treatment between March 2011 and October 2011. The healthy control subjects were recruited from hospital staff, and age/sex-matched. The diagnosis of CHF was based on the present guidelines for the diagnosis and management of CHF of the American College of Cardiology/American Heart Association and the European Society of Cardiology. CKD was defined as estimated glomerular filtration rate (GFR) at 15.0–90.0 ml/min per 1.73 m^2 of body-surface area. Type II CRS (chronic CRS) was defined as CHF that causes progressive CKD [8]. All the subjects had no evidence of gastrointestinal disease, lung disease, liver disease,

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thyroid disease, or infection. The study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Research and Ethics Committee of Changhai Hospital. Written informed consent was obtained from all subjects prior to the enrollment.

The anatomic structure of the heart and left ventricular ejection fraction (LVEF) were assessed by echocardiography. All patients received medical treatments according to the present guidelines. Specific agents included digitalis, diuretics, RAAS inhibitors, hemodialysis and β-blockers.

2.2. Hormonal assay

Blood was drawn from an antecubital vein prior to breakfast (about 6:00 AM) after an overnight fasting. Blood samples were immediately transferred to chilled polypropylene tubes containing EDTA-2Na (1 mg/ml) and aprotinin (Phoenix Pharmaceuticals; Belmont, CA, USA; 100 ml containing 0.6 trypsin inhibitor unit per milliliter blood), centrifuged at 1600 × *g* in 4 °C, and stored at −80 °C until assay.

Plasma obestatin concentration was measured using an Enzyme Linked Immunosorbent Assay Kit (R&D Systems, Inc.). No significant cross-reactivity was observed. The test range was 5–2000 pg/ml. Plasma AVP concentration was measured also using an Enzyme Linked Immunosorbent Assay Kit (R&D Systems, Inc.). The test range was 5–2000 pg/ml. Plasma concentration of brain natriuretic peptide (BNP) was measured using an Enzyme Linked Immunosorbent Assay Kit (R&D Systems, Inc.) with a test range at 10–4000 pg/ml.

Blood glucose, lipids, SCR and white blood cells (WBC) were measured in the clinical laboratory of our hospital. Plasma glucose was measured using an automated glucose oxidase method (Automatic Analyzer 7600-020, Hitachi, Tokyo, Japan). Total cholesterol (TC), triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) were measured using automatic enzymatic methods. WBC count was determined using an automated cell counter. SCR was measured using an automatic enzymatic reaction.

2.3. Statistical analysis

Numeric data are expressed as the mean ± SD. Comparison between the groups was performed with a general linear model. Post hoc analysis was conducted using the least significant difference (LSD) method. Potential relationship between plasma AVP and obestatin was examined by bivariate correlation (Pearson's correlation coefficient). *P* values less than 0.05 were considered statistically significant. All analyses were performed using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Subjects

There was no significant difference in gender, age, plasma lipids, plasma glucose and WBC count between the groups (Table 1). SCR was significantly higher in the patients with CRS than that in the patients with CHF or CKD alone, as well as in the healthy controls. SCR in patients with CKD was also higher than that in patients with CHF and the healthy controls. Plasma BNP in patients with CRS was significantly higher than that in patients with CHF or CKD alone, as well as in the healthy controls. Plasma BNP was also significantly higher in patients with CHF than in patients with CKD alone. There was no significant difference between the healthy controls and CKD. LVEF in patients with CRS was significantly lower than that in patients with CKD alone, as well as in the healthy controls. LVEF in patients with CHF was significantly lower than that in patients

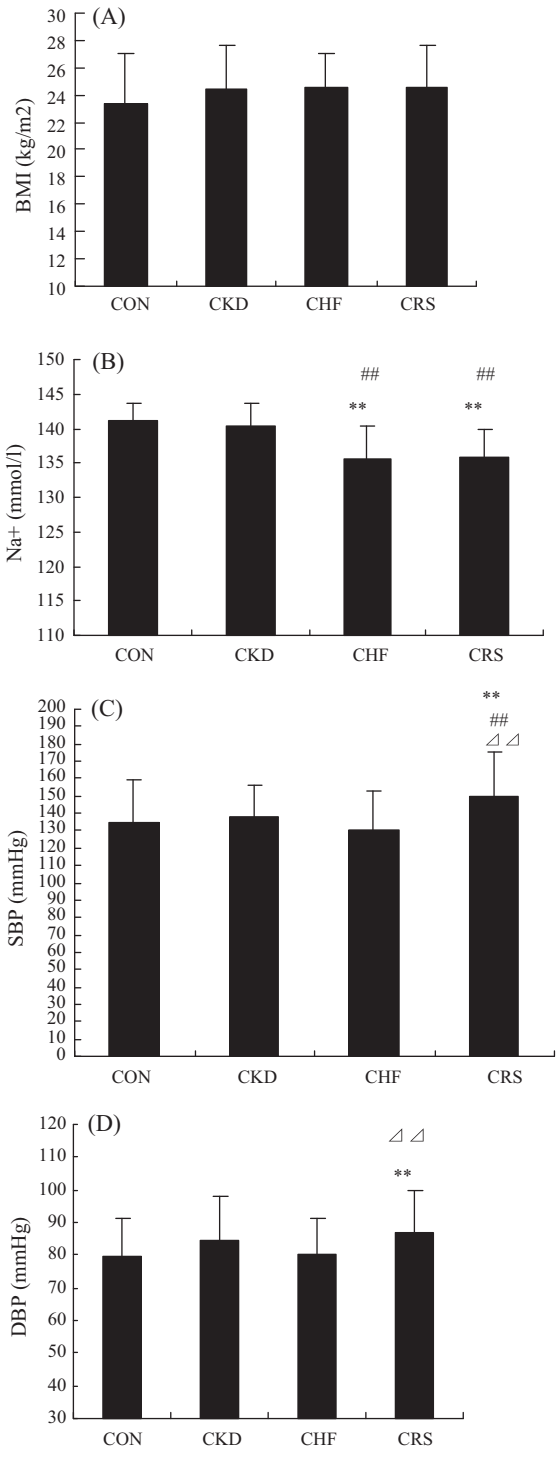

Fig. 1. (A) BMI: body mass index, (B) plasma Na^+ levels, (C) SBP: systolic pressure, (D) DBP: diastolic pressure. $^{*}P<0.05$ compared with controls; $^{**}P<0.01$ compared with controls; $^{\#\#}P<0.01$ compared with CKD; $^{\Delta\Delta}P<0.01$ compared with CHF.

with CKD alone, as well as in the healthy controls. There was no significant difference between the healthy controls and CKD. There was no significant difference between CRS and CHF (Table 1).

3.2. BMI, plasma Na^+ and blood pressure

There was no significant difference in BMI between the four groups (Fig. 1A). Plasma Na^+ in patients with CRS was significantly lower than that in the patients with CKD as well as in the healthy