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Association between N-terminal pro-brain natriuretic peptide and adiponectin in healthy Japanese men

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ABSTRACT

Background: The natriuretic peptides, brain natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP), are cardiac-derived hormones and can serve as biomarkers for ventricular dysfunction. BNP has cardio-protective effects and is known as a regulator of metabolism. In the present study, to evaluate the relationship between natriuretic peptides and metabolic disorders, we focused on the association between NT-proBNP and metabolic syndrome-related molecule adiponectin (APN).

Methods: Forty-five apparently healthy men who underwent health examination at the Osaka University Health Care Center were enrolled for this study. Physical and biochemical parameters including serum APN and NT-proBNP concentrations were obtained from all the subjects.

Results: The serum concentrations of NT-proBNP negatively correlated with metabolic disorder parameters, body mass index (BMI), waist circumferences, and fasting plasma glucose levels, but positively correlated with APN, suggesting that similar to APN, NT-proBNP is associated with metabolic disorders. Furthermore, increased serum concentrations of APN were found to be accompanied by increased serum concentrations of NT-proBNP and decreased BMI and mean intima-media thickness.

Conclusions: The serum concentrations of NT-proBNP are associated with APN concentrations and metabolic disorder parameters in healthy subjects.

1. Introduction

Brain natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) are circulating hormones that are mainly secreted from ventricular myocytes and reflect increased ventricular mechanical load and wall stress [1,2]. The levels of these peptides are elevated in patients with heart failure and can help predict the chances of mortality. Therefore, BNP and NT-proBNP serve as useful biomarkers for heart failure [2,3]. BNP binds to natriuretic peptide receptor (NPR)-A and shows various cardio-protective functions, such as diuresis, natriuresis, vasodilation and inhibitory effects on renin and aldosterone secretion, which are considered to compensate for heart failure [4].

BNP was originally considered as a cardiovascular hormone; however, a previous study reported that, by binding to NPR-A in adipocytes, BNP promotes lipolysis in human adipose tissue [5]. Accordingly, the role of BNP in metabolic regulation has been attracting attention. BNP and NT-pro BNP levels are also known to decrease in obese individuals and have an inverse relationship with body mass index (BMI), body fat mass, and body lean mass [6–8]. As BNP influences lipid and fatty acid metabolism, it has been reported that low BNP and NT-proBNP levels are associated with the metabolic syndrome and its individual components [9,10].

Adiponectin (APN) is secreted from adipocytes and has a strong relation with metabolic disorders. APN regulates insulin sensitivity, lipid metabolism, and systemic inflammation [11]. Similar to BNP and NT-proBNP, APN levels are decreased in individuals with obesity [12]. In the present study, to evaluate the role of the natriuretic peptides BNP and NT-proBNP in metabolic diseases, we focused on the association between these peptides and APN. As NT-proBNP has better stability than BNP in vitro, we measured the serum concentrations of NT-proBNP in the present study [13].

2. Methods

2.1. Study subjects

The subjects were individuals who underwent health examinations at the Osaka University Health Care Center in 2014. Forty-five

Abbreviations: BNP, brain natriuretic peptide; NT-proBNP, N terminal-pro brain natriuretic peptide; APN, adiponectin; IMT, intima-media thickness; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

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apparently healthy Japanese men (35–46 years) who were never-smokers and did not take any chronic or frequent medicine from at least 1 year before the health examinations and who did not suffer acute illness within 2 weeks before the examination were enrolled for this study. This information was obtained using questionnaires and was reconfirmed in an expert interview by trained nurses. The study was performed in accordance with the Declaration of Helsinki and the ethics guidelines for clinical research from the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology. All the experimental protocols in this study were approved by the Ethics Committee of Health Care Center, Osaka University, and written informed consent was obtained from all the subjects prior to their participation in the study.

2.2. Physical and biochemical parameters

Waist circumference (WC) at the umbilical level was measured in the late exhalation phase in the standing position. We defined abdominal obesity as WC ≥ 85 cm using the guidelines for abdominal obesity in Japanese individuals [14], and metabolic syndrome was diagnosed by abdominal obesity and the presence of two or more of the following components based on the criteria of the Japanese Society of Internal Medicine: 1) High blood pressure: systolic blood pressure (SBP) ≥ 130 mm Hg and/or diastolic blood pressure (DBP) ≥ 85 mm Hg; 2) Dyslipidemia: serum concentrations of triglycerides (TG) ≥ 1.70 mmol/l and/or low high-density lipoprotein-cholesterol (HDL-C) serum concentrations < 1.03 mmol/l; and 3) High fasting glucose: fasting plasma glucose (FPG) ≥ 6.10 mmol/l [15]. Carotid atherosclerosis was evaluated by performing ultrasound examination of the carotid artery as described previously [16]. All ultrasound examinations were performed using LOGIQ5 (GE Yokogawa Medical Systems, Tokyo, Japan), and the mean intima-media thickness (IMT) was determined using computer software that automatically traces the intima-media edge of the far wall.

Serum was collected from all the subjects after overnight fasting and kept at ≤−20 °C until assay. TG levels were measured using an enzymatic method, HDL-C and low-density lipoprotein-cholesterol (LDL-C) concentrations were measured using direct methods, FPG levels were measured using the hexokinase UV method, and HbA1c levels were measured using the latex agglutination method; the reference values were set to ≤1.68 mmol/l, 1.03–2.48 mmol/l, 1.81–3.59 mmol/l, 3.89–6.05 mmol/l, and 4.6–6.2%, respectively. APN concentration was measured using the sandwich enzyme-linked immunoassay (Otsuka Pharmaceutical Co.), and NT-proBNP concentration was measured using the electrochemiluminescene assay (Roche Diagnostics Co., Tokyo, Japan) according to the manufacturer's instructions.

2.3. Statistical analysis

Data were analyzed using SPSS Statics 19 (IBM Corp.). Kendall's rank correlation coefficient was used to analyze the variables. ANOVA with Tukey's post-hoc test was used to assess the differences between groups. Statistical significance was set at a $P < 0.05$.

3. Results

3.1. Association between APN and NT-proBNP concentrations

The characteristics of the study subjects are shown in Table 1. The subjects were all male and the mean age was 42.6 ± 4.0 year. The median serum concentrations of APN and NT-pro BNP were 7.2 (5.5–9.4) μg/ml and 19 (10–28) ng/l, respectively. As shown in Fig. 1, there was a significant positive correlation between the serum concentrations of APN and NT-proBNP ($r = 0.218$, $P = 0.038$). Table 2 shows the correlations between the serum concentration of NT-proBNP and other clinical and biochemical parameters. The serum concentration of NT-proBNP negatively correlated with body mass index (BMI), WC, and FPG ($r = -0.27$, $P = 0.01$, $r = -0.25$, $P = 0.019$, $r = -0.29$, $P = 0.006$). These data suggest that similar to APN, NT-proBNP is associated with metabolic disorder parameters.

Table 1
Characteristics of the study subjects.

n	45
Age (year)	42.6 ± 4.0
BMI (kg/m^2)	23.8 ± 2.3
WC (cm)	81.7 ± 6.3
SBP (mm Hg)	121 ± 17
DBP (mm Hg)	78 ± 12
Cr (μmol/l)	76.5 ± 9.3
TG (mmol/l)	1.03 (0.76–1.40)
HDL-C (mmol/l)	1.37 ± 0.26
LDL-C (mmol/l)	3.09 ± 0.72
FPG (mmol/l)	4.99 ± 0.61
HbA1c, %	5.3 ± 0.4
meanIMT (mm)	0.60 ± 0.08
APN (μg/ml)	7.2 (5.5–9.4)
NT-proBNP (ng/l)	19 (10–28)

Data are expressed as mean ± SD or median (interquartile range). WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; TG, triglycerides; FPG, fasting plasma glucose; IMT, intima-media thickness; APN, adiponectin; NT-proBNP, N terminal-pro brain natriuretic peptide.

3.2. Correlations between the serum concentration of NT-proBNP, mean IMT, and BMI with APN concentration

As the serum concentration of NT-pro BNP correlated with that of APN, we evaluated the relationship between NT-proBNP and other APN-related parameters. Fig. 2 shows the relation between the serum concentration of APN (tertile1 = 4.9 (4.3–5.4) μg/ml, tertile2 = 7.2 (6.6–7.7) μg/ml, and tertile3 = 11 (9.6–11.6) μg/ml) and serum NT-proBNP concentration, the mean IMT, and BMI. The serum concentrations of NT-proBNP were significantly higher in the tertile3 group than in the tertile1 group ($P = 0.033$). In addition, the BMI was significantly lower in the tertile3 group than in the tertile1 group ($P < 0.001$). The mean IMT in the tertile3 group was lower than that in the tertile1 group; however, the difference was not significant. APN is well known as a metabolic disorder-related molecule with anti-atherosclerotic effects [11,16]. Taken together, the data suggest that NT-proBNP is associated with metabolic disorder parameters thorough the increased serum concentrations of APN.

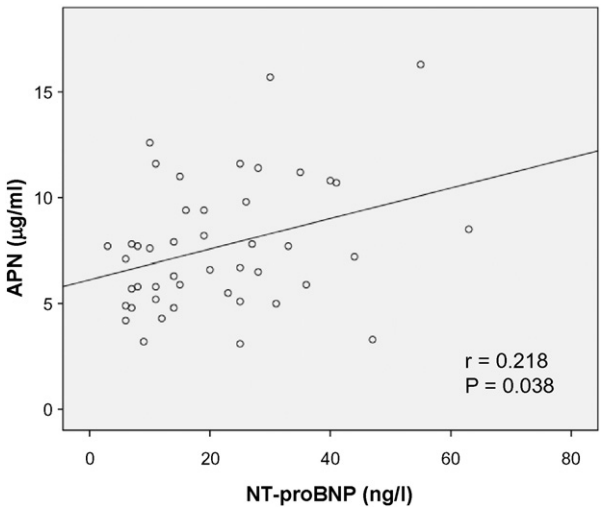

Fig. 1. Correlation between the serum concentrations of adiponectin (APN) and N terminal-pro brain natriuretic peptide (NT-proBNP).