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Plasma preptin levels are decreased in patients with essential hypertension

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The pancreatic hormone preptin amplifies glucose-mediated insulin secretion, and we investigated its circulating levels in patients with essential hypertension and possible association with carotid atherosclerosis. Ninety-eight patients were divided into hypertensive and control groups. Relationships between plasma preptin levels, clinical parameters, and carotid artery intima-media thickness (IMT) were analyzed. Plasma preptin levels were significantly lower in the hypertensive group than in the control group (1930.30±268.47 vs. 2182.88±325.81 pg/mL, $P < 0.01$). Simple linear regression analysis showed that systolic blood pressure (SBP), mean arterial pressure (MAP), and levels of serum low-density lipoprotein (LDL) and cholesterol (CHOL) were related to plasma preptin levels. Furthermore, multivariate linear regression analysis showed that SBP and serum CHOL levels were independent of plasma preptin levels, which were inversely correlated with carotid artery IMT ($r = -0.47$, $P < 0.01$) in all subjects. Plasma preptin levels of patients with carotid atherosclerotic plaques were significantly lower than those of patients without plaques (1961.69±296.07 vs. 2117.97±322.52 pg/mL, $P < 0.05$). This preliminary study revealed that plasma preptin levels are decreased in patients with essential hypertension, negatively correlated with carotid artery IMT, and significantly lower in patients with carotid atherosclerotic plaques. Therefore, decreased plasma preptin level might play a role in hypertension and its vascular complications.

1. Introduction

In recent years, humoral factors have been considered to play an important role in the pathogenesis of hypertension (Cacciapuoti 2011). A variety of vasoactive peptides such as angiotensin, adiponectin, and leptin are involved in the pathogenesis of hypertension (Young et al. 2015; Kim et al. 2013). The imbalance between these endogenous vasoactive peptides may cause vasomotor disturbances, elevated blood pressure, and even increase the risk of cardiovascular morbidity and mortality (Sabbatini et al. 2015; Kawarazaki et al. 2016).

Preptin is a 34-residue hormone that is co-secreted with insulin and amylin by pancreatic islet β cells (Buchanan et al. 2001). It preptin is also expressed in the salivary gland, mammary tissue, and kidneys (Buchanan et al. 2001; Aydin et al. 2013, 2014). Studies have verified that preptin acts as a physiological amplifier of glucose-mediated insulin secretion through the insulin-like growth factor 2 receptor (IGF2R) (Buchanan et al. 2001; Cheng et al. 2012). Furthermore, preptin regulates bone anabolism by dose-dependently stimulating the proliferation of osteoblasts and reducing osteoblast apoptosis (Cornish et al. 2007; Li et al. 2013; Kowalczyk et al. 2014). In patients with diabetes mellitus and polycystic ovarian syndrome (PCOS), plasma preptin levels are elevated and significantly correlated with the systolic (SBP) and diastolic (DBP) blood pressure (Abd El Dayem et al. 2015; Yang et al. 2009; Bu et al. 2012). However, currently, the role of preptin in cardiovascular disease (CVD), especially in essential hypertension, and the related vascular complications remain unclear.

This study aimed to investigate circulating preptin levels in essential hypertensive patients and the possible association between plasma preptin levels and carotid atherosclerosis. Therefore, the plasma preptin level and its relationships with clinical parameters and carotid artery intima-media thickness (IMT) were analyzed in patients with essential hypertension. Furthermore, plasma preptin levels in patients with and without carotid atherosclerotic plaques were compared.

2. Investigations and results

2.1. Clinical characteristics of patients

The clinical characteristics of the two groups of patients are listed in Table 1. Compared with the control group, the hypertensive group showed significantly increased SBP, DBP, mean arterial pressure (MAP), and carotid artery IMT ($P < 0.01$). Furthermore, the fasting serum glucose (FSG), Creatinine high-density lipoprotein (HDL) levels triglyceride (TG) and white blood cell count of patients with hypertension were higher than those of the control patients ($P < 0.05$).

Table 1: Clinical characteristics between the control group and the hypertensive group

	control group (n=38)	hypertensive group (n=60)
Age, years	59.94±10.23	60.07±11.01
Gender (Male/Female, n)	22/16	33/27
BMI, kg/m²	22.67 ±3.41	23.53±1.99
SBP, mmHg	117.50±8.76	163.13±23.68**
DBP, mmHg	76.03±6.22	93.30±13.87**
MAP,mmHg	89.85±5.74	116.58±15.36**
FSG, mmol/L	5.29 (5.05-5.59)	5.67 (5.13-6.46)*
Uric acid, μmol/L	291.68±86.67	315.86±88.17
Blood urea nitrogen, mmol/L	4.84 (4.05-5.50)	5.25 (4.03-6.34)
Creatinine, μmol/L	66.60±14.94	76.12±20.12*
HDL, mmol/L	1.25 (1.10-1.53)	1.20 (1.01-1.36)*

	control group (n=38)	hypertensive group (n=60)
LDL, mmol/L	2.90±0.87	2.96±0.90
TG, mmol/L	1.28±0.66	1.84±1.57*
CHOL, mmol/L	4.89±1.05	4.84±1.21
WBC count,10^9/L	5.86 (4.85-7.14)	6.43 (5.62-8.34)*
carotid artery IMT, mm	0.80 (0.70-0.90)	1.20 (1.10-1.48)**

**$P < 0.01$ compared with control group; *$P < 0.05$ compared with control group;
BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FSG, fasting serum glucose; HDL, high-density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; CHOL, cholesterol; WBC, White blood cell; IMT, carotid artery intima-media thickness

2.2. Plasma preptin levels of patients with essential hypertension

The patients in the essential hypertension group had a fasting plasma preptin level of 1930.30±268.47 pg/ml, which was significantly lower than that of the control group (2182.88±325.81 pg/mL, $P < 0.01$, Fig. 1A). Furthermore, the median serum homocysteine level was significantly higher in the essential hypertension group than in the control group [15.50 (range, <12.15-20.95 μmol/L) *vs*. 12.45 (range, <10.18-15.98 μmol/L)L, $P < 0.01$, Fig. 1B].

2.3. Association between plasma preptin level and clinical parameters

The simple linear regression analysis showed that age, SBP, MAP, and serum LDL and CHOL levels were related to plasma preptin levels (Table 2). Moreover, the multivariate linear regression analysis demonstrated that the SBP and serum CHOL levels were independently associated with plasma preptin levels (Table 3). The multiple regression equation was: *Y*preptin = 2075.71- 2.95SBP+ 80.09CHOL.

Table 2: Simple linear regression analysis of variables associated with plasma preptin in all subjects

Independent variable	Unstandardized coefficients		*P*
	B	Std. Error	
BMI	-8.94	12.13	0.463
SBP	-2.79	1.06	0.009
DBP	-4.39	2.21	0.050
MAP	-4.29	1.73	0.015
FSG	-15.76	17.60	0.373
Uric acid	-0.30	0.37	0.426
Blood urea nitrogen	9.16	17.90	0.610
Creatinine	-0.55	1.73	0.752
HDL	164.68	123.35	0.185
LDL	76.10	35.70	0.036
TG	14.82	24.40	0.607
CHOL	77.73	26.87	0.005
WBC count	17.94	12.01	0.139

BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FSG, fasting serum glucose; HDL, high-density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; CHOL, cholesterol; WBC, White blood cell

Table 3: Multiple stepwise regression analysis of variables associated with plasma preptin in all subjects

Independent variable	Unstandardized coefficients		*P*
	B	Std. Error	
(constant)	2075.71	186.43	0.000
SBP	-2.95	1.000	0.003
CHOL	80.09	25.81	0.004

SBP, systolic blood pressure; CHOL, cholesterol

2.4. Association between plasma preptin levels and carotid artery IMT

Spearman analysis showed that plasma preptin levels were negatively correlated with the carotid artery IMT (r = -0.47, $P < 0.01$, Fig. 2C), which was measured by carotid ultrasonography.

2.5. Plasma preptin levels in the group of patients with carotid atherosclerosis

Carotid atherosclerotic plaques were also detected by carotid ultrasonography (Fig. 2A and B). Based on this finding, the patients were divided into two groups consisting of those with and without carotid atherosclerotic plaques. The plasma preptin levels of patients with carotid atherosclerotic plaques were significantly lower than those of the group without plaques (1961.69±296.07 and 2117.97±322.52 pg/mL, $P < 0.05$, Fig. 2D).

3. Discussion

Hypertension is a major risk factor for stroke and coronary heart disease, and monitoring blood pressure (BP) is the key to preventing CVD. BP is regulated by the balance between levels of vasoactive peptides, including nitric oxide (NO), adrenomedullin, angiotensin II, and salulin (Young et al. 2015; Gkaliagkousi et al. 2009; Kato et al. 2006; Watanabe et al. 2008). Adipokines such as adiponectin, leptin, and resistin and gut hormones including

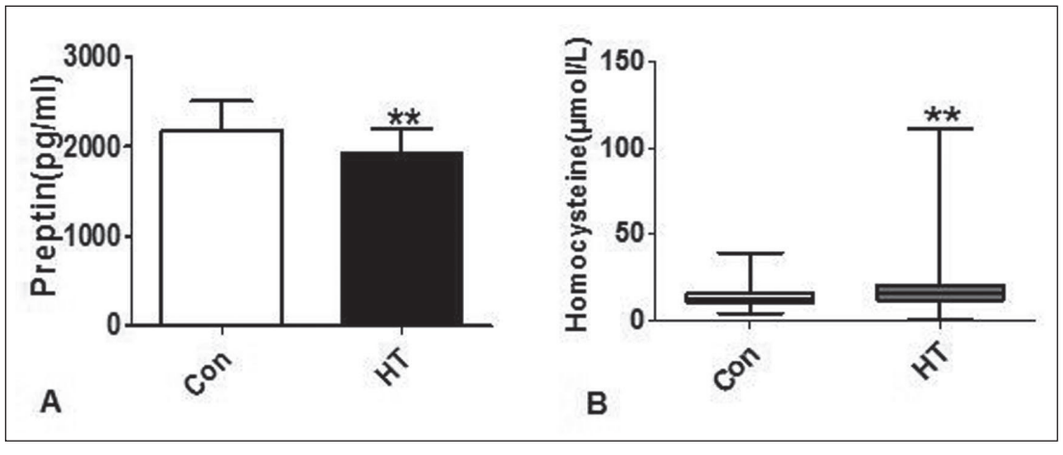

Fig. 1: Plasma preptin level (A) and serum homocysteine level (B) in the control group and hypertensive group. (Con, control group, n=38; HT, hypertensive group, n=60)
**$P < 0.01$ compared with control group; * $P < 0.05$ compared with control group.

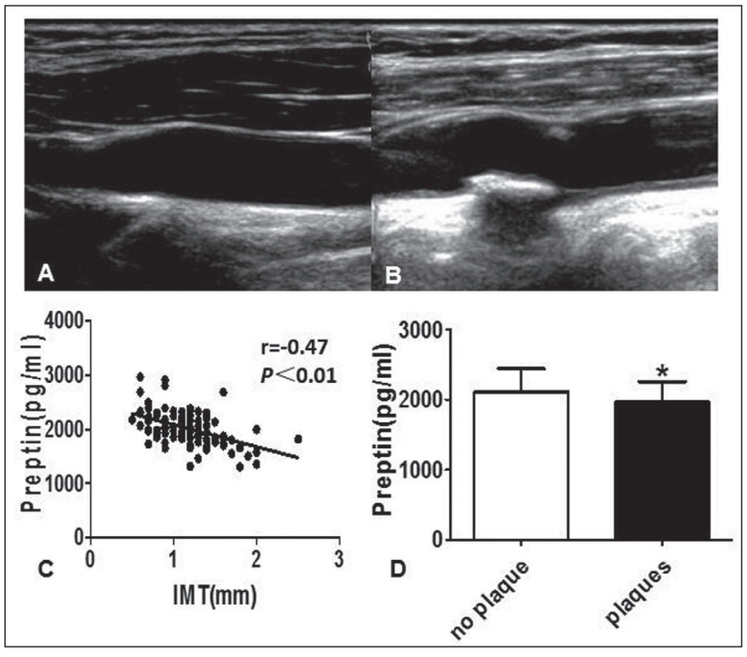

Fig. 2: Ultrasound images of normal carotid (A) and carotid atherosclerotic plaque (B). Relationship between plasma preptin level and carotid IMT in all subjects (C). Plasma preptin level in the groups with carotid artery plaque and without plaque (D). (no plaque, the group without carotid artery plaque, n=42; plaques, the group with carotid artery plaque, n=56) • All subjects
$^{**}P < 0.01$ compared with control group; $^{*}P < 0.05$ compared with control group.

ghrelin and nesfatin are also involved in the pathogenesis of essential hypertension and its vascular complications (Rodríguez et al. 2010; Yamawaki et al. 2012). However, the potential role of preptin, a pancreatic hormone, in essential hypertension and its vascular complication remain unclear.

Preptin, a novel 34-amino acid peptide (3984 Da), was purified from pancreatic βTC6-F7 islet β-cell granules (Kim et al. 2013). It is derived from proinsulin-like growth factor II (proIGF-II) and co-secreted with insulin and amylin (Buchanan et al. 2001; Cheng et al. 2012). Increasing evidence indicates that preptin activates the insulin-like growth factor 2 receptor (IGF2R) linked to the protein kinase C (PKC)-phospholipase C pathway to induce calcium-dependent insulin secretion under high glucose conditions (Buchanan et al. 2001; Cheng et al. 2012). The plasma preptin level is abnormally elevated in overweight adults, as well as in patients with obesity, impaired glucose tolerance, type 1 and type 2 diabetes mellitus, and gestational diabetes (Abd El Dayem et al. 2015; Yang et al. 2009; Bu et al. 2012; El-Eshmawy et al. 2015). Furthermore, the levels of preptin are significantly decreased in patients with psoriasis who have low homeostatic model assessment-insulin resistance (HOMA-IR) indices (Dogan et al. 2016). Bu et al. (2012) found a positive correlation between preptin levels and HOMA-IR values, indicating that preptin may play a role in the pathogenesis of insulin resistance and metabolic syndrome without affecting insulin secretion.

Recent studies have revealed that the plasma preptin level is associated with BP in patients with diabetes. Abd El Dayem et al. (2015) reported that preptin levels had a significant positive correlation with SBP in 62 adolescent patients with a duration of type 1 diabetes < 5 years. Yang et al. (2009) found that plasma preptin levels were positively correlated with DBP in patients with impaired glucose tolerance and type 2 diabetes. However, Wang et al. (2017) observed no significant difference in preptin levels between women with preeclampsia and those with normal pregnancies. Hence, circulating preptin levels in human hypertension need to be explored.

In the present study, plasma preptin levels were significantly decreased in the essential hypertension group compared with those in the control group. Moreover, the simple and multiple stepwise linear regression analyses showed that SBP was independently associated with plasma preptin levels. These results indicate that preptin might be involved in the development of essential hypertension. However, our observations are not consistent with those of previous studies on diabetes and women with preeclampsia (Abd El Dayem et al. 2015; Yang et al. 2009; Wang et al. 2017) . This disparity might be related to insulin resistance, hyperglycemia, hyperinsulinemia, different study designs, and different groupings. Furthermore, we found that the fasting plasma preptin level was associated with SBP, MAP, and serum LDL and CHOL levels in the simple linear regression analysis. Moreover, the multiple stepwise regression analysis revealed that SBP and CHOL levels were independently related to plasma preptin levels. These results suggest a potential link between preptin levels, lipid metabolism, and BP, which are closely related to atherosclerosis. Therefore, the relationships between plasma preptin levels and carotid artery IMT were analyzed, and the plasma preptin levels in patients with and without carotid atherosclerotic plaques were compared.

Carotid artery IMT is a non-invasive marker of preclinical atherosclerosis, which is associated with CVD risk factors and outcomes (Cao et al. 2007). Long-term hypertension induces vascular remodeling, including atherosclerosis, vascular stenosis, and occlusion, which lead to the incidence of adverse cardiovascular events (Turin et al. 2016; Lackland et al. 2015). The present study showed that plasma preptin level was negatively correlated with carotid artery IMT. The plasma preptin level of patients with carotid atherosclerotic plaques was significantly lower than that of the group without plaques. Based on these findings, we speculated that preptin might be involved in the progression of atherosclerosis or the vascular complications of hypertension.

Recent evidence supports the notion that crosstalk exists between atherosclerosis and osteoporosis (Kang et al. 2015; Issever et al. 2013). In men with osteoporosis and patients with osteopenia, plasma preptin levels are decreased and positively correlated with bone formation indices, including bone alkaline phosphatase, bone Gla protein, and procollagen type I amino-terminal propeptide (Li et al. 2013). Moreover, preptin might regulate bone anabolism to dose-dependently stimulate the proliferation of osteoblasts and reduce osteoblast apoptosis, which increased bone area and mineralizing surface in adult mice (Cornish et al. 2007; Li et al. 2013; Kowalczyk et al. 2014). The underlying mechanism might be related to upregulation of the extracellular signal-regulated kinase (ERK)/connective tissue growth factor (CTGF) pathway in human osteoblasts (Liu et al. 2010). These studies and our present observations indicate that low plasma preptin levels might participate in the progression of carotid atherosclerosis by regulating bone anabolism combined with specific receptors. However, further research is required.

Some of the limitations of the present study need to be mentioned. For example, only a small number of patients with essential hypertension were included. In addition, the relationship between preptin levels and the progression of hypertension and atherosclerosis was not studied in detail. In the future, our group plans to conduct in-depth mechanistic studies to investigate the role of preptin in hypertension, vascular remodeling, and atherosclerosis.
In summary, this study demonstrated that plasma preptin levels were decreased in patients with essential hypertension. In addition, plasma preptin levels showed a negative correlation with carotid artery IMT and were significantly lower in patients with carotid atherosclerotic plaques than in those without plaques. These findings suggest that decreased plasma preptin level might play a potential role in hypertension and its vascular complications.

4. Experimental

4.1. Subjects

The study population consisted of 98 patients divided into the essential hypertension and control groups (n = 60 and 38, respectively) with a mean age of 60.07±11.01 and 59.94±10.23 years, respectively. Patients were defined as hypertensive when their clinical BP was ≥ 140/90 mmHg, and the severity was defined according to the European Society of Hypertension (ESH) guidelines of 2007 (Mancia et al. 2007). The clinical BP was calculated as the average of three consecutive measurements using an automatic sphygmomanometer after the subject had been sitting for 5 min. Patients with secondary hypertension were excluded from the study. In addition, the 60 patients did not have concomitant diseases such as diabetes, renal failure, coronary heart disease, and stroke. The possibility that the control patients had hypertension, metabolic syndrome, diabetes, or other CVDs was also ruled out based on their medical history, and results of physical examination, laboratory tests, and electrocardiographic (ECG) examination. They were instructed not to smoke, drink alcohol, and eat high-fat food for 12 h immediately prior to the study. The present study was approved by the ethics committee of The Fourth Hospital of Harbin Medical University, Harbin, P. R. China. All patients enrolled in the present study provided informed consent.

4.2. Data collection

Blood samples were collected in tubes containing disodium ethylenediaminetetraacetate dihydrate (Na_2-EDTA, 1 mg/mL) and 500 kIU/mL aprotinin (Sigma, St. Louis, MO, USA) in the morning after an overnight fast. The plasma was obtained by centrifugation at 3000 rpm for 10 min at 4°C, and the samples were stored at -80°C until the analysis.
Fasting serum glucose, lipid profile, serum creatinine, blood urea, serum uric acid, and homocysteine levels were measured using an automatic analyzer (Cobas 8000, Roche, Switzerland). The concentration of plasma preptin was measured in samples extracted using a Sep-Pak C18 cartridge and assayed using a radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals Inc., Belmont, CA, USA).

4.3. Carotid ultrasonography

Carotid ultrasonography was performed to evaluate carotid artery atherosclerosis by measuring the mean common carotid artery (CCA) IMT and detecting the deposited plaque. High-resolution B mode, color Doppler, and pulse Doppler ultrasonography of both carotid arteries were performed using an ultrasound scanner (GE, Vivi E9 ultrasound system, USA) equipped with a 7.5-MHZ linear array transducer by the same experienced sonographer. Patients were examined in the supine position with their heads tilted backward. After the carotid arteries were located by transverse scans, the probe was rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. The high-resolution images of the far wall of the bilateral CCA, internal carotid arteries (ICA), and carotid bulbs were acquired according to recommendations of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force (Stein et al. 2008). The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. At least three measurements were taken over a 1-cm length of the far wall of each CCA segment, and the measurements of both sides were averaged to obtain the IMT. When plaque was present in the segment where the IMT was measured, the plaque thickness was averaged in the IMT measurement. The plaque was defined as a focal IMT ≥ 1.5 mm (Ikeda et al. 2012).

4.4. Statistical analysis

In the present study, all the statistical analyses were performed using the statistical package for the social sciences (SPSS) 23.0 software (SPSS Inc., Chicago, IL, USA). The data are shown as the means ± standard deviation or medians (interquartile range) for continuous variables. The differences between two groups were analyzed by the Student's *t*-test or Mann-Whitney's U test for continuous variables.
Associations between the plasma preptin levels or serum homocysteine levels and carotid artery IMT were evaluated by the Spearman correlation test. Simple and multiple linear regression analyses were performed to examine the association between plasma preptin levels and other variables. All of the statistical analyses were two-sided, and a $P < 0.05$ was considered to indicate statistically significant data.
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Conflicts of interest: None declared.

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