Peptides 46 (2013) 167–171

Contents lists available at SciVerse ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Decreased plasma nesfatin-1 levels in patients with acute myocardial infarction

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ARTICLE INFO

Article history:
Received 14 April 2013
Received in revised form 5 June 2013
Accepted 5 June 2013
Available online 24 June 2013

Keywords:
Nesfatin-1
Acute myocardial infarction
Angina pectoris
Angiography

ABSTRACT

Nesfatin-1 is a novel anorexigenic hormone which has close relationship with diabetes, obese, anorexia nervosa, psychiatric disorders and neurogenic diseases. The aim of our study was to evaluate levels of plasma nesfatin-1 among patients presenting with coronary artery disease and the correlation between nesfatin-1 levels and other clinical parameters. Fasting plasma levels of nesfatin-1 were tested in 48 acute myocardial infarction (AMI) patients, 74 stable angina pectoris (SAP) patients and 34 control subjects. All of them were examined by coronary angiography. The severity of coronary atherosclerosis was assessed using the Gensini score. Plasma nesfatin-1 levels were significantly lower in AMI group than SAP group or control group (0.91 ± 0.08 ng/mL vs. 0.98 ± 0.19 ng/mL and 1.09 ± 0.39 ng/mL, respectively, $P < 0.05$). In AMI patients, plasma nesfatin-1 levels were negatively correlated with high-sensitivity C-reactive protein, neutrophil% or Gensini scores. Such information implies that lower nesfatin-1 concentration may play a very important role in the development of AMI.

1. Introduction

Nesfatin-1 is a novel hypothalamus nucleobindin 2 (NUCB2)-derived peptide that is distributed in several regions including arcuate nuclei, paraventricular nuclei, supraoptic nuclei, and lateral hypothalamicareas [16,27]. The mRNA expression of nesfatin-1 is significantly decreased by fasting and significantly increased in the hypothalamus on refeeding [12]. Intracerebroventricular injection of this peptide to rats or intraperitoneal application to mice reduced food intake [16,21] suggesting that nesfatin-1 is an anorexigenic hormone. In addition to its regulation of food intake, its relationship with clinical diseases has also been investigated in recent years. For example, Li et al. found that plasma nesfatin-1 levels were significantly lower in type 2 diabetes mellitus (T2 DM) patients compared to healthy subjects and type 1 DM patients [13]. The cerebrospinal fluid (CSF)/plasma nesfatin-1/NUCB-2 ratio was found to be significantly negatively associated with body mass index (BMI), bodyweight, fat mass, and CSF glucose in obese humans [23]. Zegers et al. found that several SNPs (including rs214101, rs757081–rs1330: CA, rs214101–rs214086–rs1330: TCG, et al.) were associated with BMI, weight and fat free mass in the male population [29]. Its relationship with psychiatric disorders and neurogenic diseases were also studied. Increased plasma levels of this peptide were found in patients with major depressive disorder [2] or epilepsy [3], and decreased levels were found in patients with generalized anxiety disorder [9].

Previous studies have found that some appetite-regulating peptides have a range of effects on the cardiovascular system and play important roles in the pathogenesis of coronary artery disease (CAD). Leptin, an appetite-inhibiting peptide, could exert many potentially atherogenic effects such as induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation, and migration, hypertrophy and proliferation of vascular smooth muscle cells [5]. Plasma levels of leptin increased in acute myocardial infarction (AMI) patients, and correlated negatively with left ventricular ejection fraction [11]. Ghrelin, an appetite-stimulating hormone, decreases sympathetic activity, produces vasodilation and has an anti-inflammation function in the vasculature [20]. Its concentrations were considerably lower in CAD patients with respect to the control group [10]. As a novel anorexic peptide, studies about nesfatin-1's cardiovascular function are limited, but the results are promising. Angelone et al. identified the presence of both nesfatin-1 protein and NUCB2 mRNA in rat cardiac extracts and found that exogenous nesfatin-1 could depress contractility and relaxation on isolated and Langendorff-perfused rat heart preparations [1]. Central nesfatin-1 was shown to activate the nervous circuits that are

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http://dx.doi.org/10.1016/j.peptides.2013.06.006

responsible for hypertension [14], an effect which is presumed to occur via hypothalamic melanocortin-3/4 receptors [28].

The aims of our study were to evaluate levels of plasma nesfatin-1 among patients presenting with CAD and whether there were correlations between nesfatin-1 levels and coronary Gensini scores, as well as with other clinical parameters.

2. Methods

2.1. Study population

A total of 156 subjects admitted to the Cardiology Department at Qingdao Municipal Hospital for coronary angiography owing to AMI ($n = 48$), stable angina pectoris (SAP, $n = 74$) or a clinical suspicion of CAD in subjects with multiple coronary risk factors but without lesions on angiography (served as controls, $n = 34$) were enrolled for the study. Exclusion criteria included age of more than 80 or less than 40, congenital heart disease, surgery or trauma 1 month before the study, known cardiomyopathy, rheumatic heart disease, overt congestive heart failure, known malignant diseases, febrile conditions, acute or chronic inflammatory disease, psychiatric disorders, neurogenic diseases, renal insufficiency and abnormal liver function.

Data on demographic factors, BMI, history of risk factors, smoking habits, family history of cardiovascular disease in first-degree relatives were recorded. BMI was measured in kilograms per meters squared. Cigarette smoking was recorded as smoking index (defined as the number of cigarette-years smoked). Hypertension was defined as resting systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or the use of any antihypertensive agent. All study participants underwent a standard clinical examination. The AMI and SAP subjects were receiving identical drug therapy including aspirin, angiotensin converting enzyme inhibitors, nitrates, heparin, β-blockers or statins.

The study was approved by the Institutional Ethics Committee. Before participation in the study, informed written consent was obtained from each subject after explaining the protocol.

2.2. Sampling

Venous blood was collected in the morning from the subjects who fasted overnight from a forearm vein into plain sterile tubes for serum and into ethylenediaminetetraacetic acid (EDTA) tubes for plasma just before the angiography. Blood samples used for nesfatin-1 examination were placed in EDTA tubes containing 500 Kallikrein inactivation unit (KIU) aprotinin to prevent digestion of peptides by proteases. Serum and plasma were separated and stored at −80 °C for further analysis.

2.3. Measurement

Fasting plasma nesfatin-1 levels were measured using a commercial enzyme linked immunosorbent assay kit (Phoenix Pharmaceuticals, Belmont, CA, USA), with a measurement interval of 0.78–50 ng/mL. All samples from one subject were run in duplicate in the same assay. The measurement of blood glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and routine blood test were performed using standard laboratory methods. High-sensitivity C-reactive protein (hs-CRP) was evaluated using immunoturbidimetry. Insulin was tested using an electrochemiluminescence immunoassay. The homeostasis model of assessment- insulin resistance index (HOMA-IR) was calculated for each patient using the formula [fasting glucose (mmol/L) × fasting insulin (lU/mL)/22.5].

Table 1
Demographic characteristic of patients with AMI, SAP and healthy subjects.

Variables	AMI ($n = 48$)	SAP ($n = 74$)	Control ($n = 34$)
Age (year)	63.8 ± 11.2	62.1 ± 9.3	60.8 ± 10.7
Male (%)	36(75)	54(73)	24(71)
BMI (kg/m^2)	27.9±6.0	26.2 ± 3.8	27.8 ± 3.7
SBP (mmHg)	124.6 ± 22.0[a]	139.9 ± 22.0	134.7 ± 19.5
DBP (mmHg)	76.9 ± 11.7	79.8 ± 9.2	78.8 ± 9.9
FBG (mmol/L)	7.4 ± 3.1[a]	5.4 ± 1.4[c]	6.2 ± 1.6
TG (mmol/L)	2.2 ± 1.4	3.1 ± 8.2	1.4 ± 0.6
TC (mmol/L)	4.9 ± 1.5[a]	4.6 ± 2.3	4.5 ± 1.2
LDL (mmol/L)	2.86 ± 0.6[a]	2.38 ± 1.1	2.49 ± 0.7
HDL (mmol/L)	1.24 ± 0.3	1.22 ± 0.3	1.23 ± 0.2
WBC (×10^9/L)	8.8 ± 2.9[a,b]	6.7 ± 1.6	6.6 ± 1.0
N%	65.0 ± 15.1[a,b]	56.6 ± 14.1	51.5 ± 9.0
hs-CRP (mg/L)	21.2 ± 30.1[a,b]	2.4 ± 2.2	1.9 ± 0.6
Insulin (lU/mL)	15.3 ± 29.9	11.8 ± 18.1	9.3 ± 6.5
HOMA-IR	4.4 ± 7.4	3.1 ± 5.4	2.6 ± 1.8
Smoke index	329.2 ± 371.0	241.2 ± 311.7	256.3 ± 314.2
Gensini score	15.7 ± 9.9[a,b]	12.9 ± 11.4	0.0 ± 0.0
Family history (%)	14(29)	21(28)	10(29)
Hypertension (%)	28(58)	54(73)	24(71)
Diabetes (%)	10(21)	24(32)	14(41)

[a] $P < 0.05$, compared with SAP.
[b] $P < 0.05$, compared with control.
[c] $P < 0.05$, compared with control.

2.4. Coronary angiography and Gensini score

Coronary angiograms were obtained according to standard techniques. The severity of coronary atherosclerosis in patients was assessed using the Gensini score [8], which grades narrowing of the lumen of the coronary arteries. The score was given as 1 for 1–25% narrowing, 2 for 26–50% narrowing, 4 for 51–75% narrowing, 8 for 76–90% narrowing, 16 for 91–99% narrowing and 32 for total occlusion. The score is then multiplied by a factor that takes into account the importance of the lesion's position in the coronary arterial tree, for example, 5 for the left main coronary artery, 2.5 for the proximal left anterior descending coronary artery (LAD) or proximal left circumflex coronary artery (LCX), 1.5 for the mid-region of the LAD, and 1 for the distal LAD or mid-distal region of the LCX. Gensini score was expressed as the sum of the scores for all of the coronary arteries.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS 20.0(SPSS Inc.). The Kolmogorov–Smirnov Z test showed that some data were not normally distributed. Therefore, for these irregularly distributed data, the Kruskal–Wallis test was employed for between-group comparisons, and the pairwise comparison test was used for two-way comparisons in groups where statistical significance was established. Those with normally distributed variables were analyzed with one-way ANOVA and LSD or Tamhane test. Data were presented as the means ± SEM. Correlations between variables were analyzed with Pearson's coefficient. A P value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline clinical and laboratory characteristics

The clinical and laboratory features of the subjects are shown in Table 1. The three study groups were comparable with respect to age, gender, BMI, DBP, TG, HDL, insulin, HOMA-IR, Smoke index, family history and history of hypertension or diabetes ($P > 0.05$). The AMI group had significantly lower levels of SBP but higher levels of fasting blood glucose (FBG), LDL, white blood cell (WBC) count,