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Serum levels of fatty acid binding protein 4 and fat metabolic markers in relation to catecholamines following exercise

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ABSTRACT

Background: Lipolysis is stimulated by activation of adrenergic inputs to adipose tissues. Our recent study showed that serum concentrations of fatty acid binding protein 4 (FABP4) are robustly elevated in patients with acute myocardial infarction and ventricular tachyarrhythmia, that display a marked activation of the sympathetic nervous system (SNS). However, it remains unknown whether circulating FABP4 concentrations are associated with exercise-induced SNS activation.

Methods: Thirty one healthy volunteers underwent cardiopulmonary exercise testing on a cycle ergometer up to the workload levels below and above anaerobic threshold, low- and high-intensity exercise, respectively. Serial blood samplings were performed before and after exercise.

Results: High-intensity exercise significantly increased serum concentrations of FABP4 and catecholamines, and their concentrations declined fast thereafter in a similar fashion. These changes were accompanied by little, if any, changes in other metabolic markers. Regardless of adiposity, percent change from baseline to peak FABP4 levels (%FABP4) was comparable in all subjects. Stepwise regression analysis revealed that %FABP4 was highly correlated with that in norepinephrine.

Conclusions: Our study reveals the significant correlation between circulating FABP4 and norepinephrine levels during exercise testing. Together with the fact that FABP4 is secreted from adipocytes via β-adrenergic-mediated lipolytic mechanisms, this study suggests FABP4 as a potential biomarker for adrenergic overdrive.

1. Introduction

Fatty acid binding protein 4 (FABP4, also known as adipocyte FABP or aP2) is a member of the cytosolic fatty acid binding protein family and highly expressed in adipocytes and macrophages [1]. FABPs bind to hydrophobic ligands such as long chain fatty acids (FA) with high affinity. It has been proposed that biological function of FABPs is trafficking of FA to subcellular compartments. Clinical and animal-based studies have demonstrated that FABP4 has an important role in obesity-related metabolic diseases such as insulin resistance, type 2 diabetes, hepatosteatosis and atherosclerosis [2,3].

Recently, FABP4 has also been introduced as a fat-derived circulating protein. Serum FABP4 levels are strongly correlated with adiposity while FABP4 is eliminated from the circulation mainly by renal clearance [3,4]. Secretion of FABP4 from adipocytes is enhanced by lipolysis, which is mainly activated by catecholamines during activation of sympathetic nervous system (SNS). Catecholamines stimulate β1/2/3-adrenergic receptor-mediated adenyl cyclase-protein kinase A (βAR/AC/PKA) pathway, which in turn promotes lipolysis via activation of several cytosolic lipases [5,6]. Emerging evidence has demonstrated that serum FABP4 levels are positively correlated with markers of the metabolic syndrome and vascular diseases and that an increase in serum levels of FABP4 at baseline predicts the risk for metabolic and vascular morbidity and mortality [3]. These findings suggest that circulating FABP4 derived from adipocytes is a useful biomarker to estimate current status of cardiometabolic diseases and predict their incidence in the future.

We recently found that serum FABP4 concentrations are also

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Table 1
Background of the subjects at baseline.

Subjects (male/female)	31 (19/12)
Age (years)	23 (22–25)
Height (cm)	167.6 ± 7.9
Body weight (kg)	58.0 (51.0–64.0)
Body mass index (kg/m^2)	20.5 (19.6–21.9)
Heart rate (bpm)	71.0 ± 8.0
Systolic blood pressure (mm Hg)	121.0 ± 12.4
Creatinine (mg/dl)	0.78 ± 0.19
eGFR (ml/mi/1.73m^2)	94.4 ± 16.9
Glucose (mg/dl)	87 (82–91)
TG (mg/dl)	90 (59–124)
FABP4 (ng/ml)	9.0 (5.6–12.3)

Values represent number of subjects or mean ± SD or median (interquartile range).

dynamically regulated during early phase of acute myocardial infarction (AMI). In patients with AMI, serum FABP4 concentrations peaked on admission or just after percutaneous coronary intervention and declined thereafter [7]. Of note, FABP4 concentrations were particularly elevated in patients with AMI resuscitated from out-of-hospital cardiac arrest (median 130.2 ng/ml, interquartile range 51.8–243.9 ng/ml) compared with those without (median 26.1 ng/ml, interquartile range 17.1–43.4 ng/ml). Together with previous notion that ischemia and lethal arrhythmia are strongly associated with activation of SNS via elevated levels of epinephrine and norepinephrine [8–10], these findings allowed us to presume a scenario that severe acute cardiac events induce robust activation of SNS, which in turn promotes lipolysis of TG in adipocytes, leading to rapid and dynamic secretion of FABP4 into circulation. To our knowledge, however, the hypothesis of direct link between dynamic change of circulating FABP4 and activation of SNS in physiological situations has not been investigated at least in human populations.

In this study, we address the question of whether physiological activation of SNS by exercise increases serum FABP4 levels and whether such an increase in FABP4 levels is quantitatively correlated to plasma catecholamine levels in humans. Our data clearly demonstrate that circulating FABP4 levels following high-intensity exercise on a cycle ergometer are significantly correlated with norepinephrine, a finding which supports FABP4 as a potential biochemical marker for generalized SNS activation.

2. Materials & methods

2.1. Study subjects

Thirty one subjects (male/female, 19/12) between the ages of 21–33 years old were recruited from Gunma University campus community (Table 1). Their health condition, past history and family history were checked by medical questionnaire. They were basically healthy with no limitation of exercise, but a few people had minor health problems including allergic rhinitis, atopic dermatitis and bronchial asthma under good control. They had no hypertension, renal dysfunction and diabetes. Written informed consent was received from all subjects.

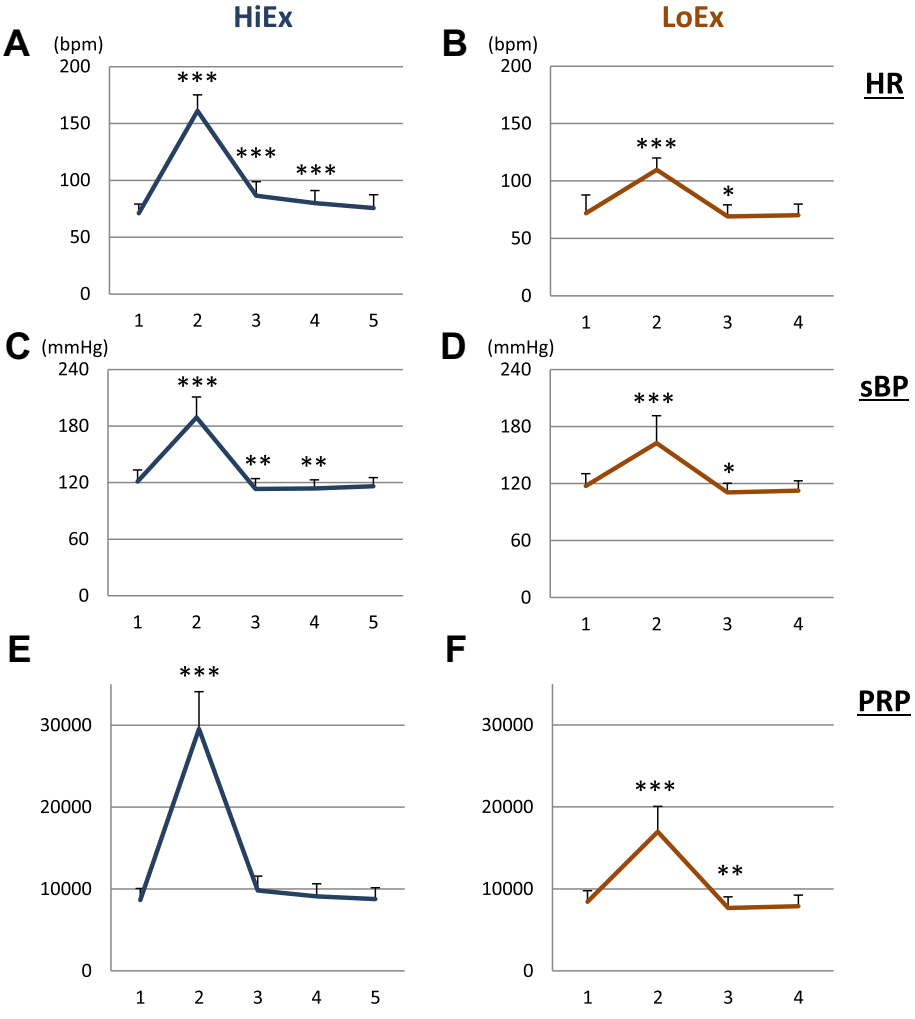

Fig. 1. Hemodynamic changes before and after HiEx and LoEx. Time course; 1, at the baseline; 2, at peak; 3, 10 min after Ex; 4, 20 min after Ex; 5, 40 min after Ex. The values at the baseline were compared with the data at each time point after exercise. p vs. the value at the baseline, * < 0.05, ** < 0.01, *** < 0.001.