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The interface of hypothalamic–pituitary–adrenocortical axis and circulating brain natriuretic peptide in prediction of cardiopulmonary performance during physical stress

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ABSTRACT

Brain natriuretic peptide (NT-pro-BNP) was implicated in the regulation of hypothalamic–pituitary–adrenocortical (HPA) responses to psychological stressors. However, HPA axis activation in different physical stress models and its interface with NT-pro-BNP in the prediction of cardiopulmonary performance is unclear. Cardiopulmonary test on a treadmill was used to assess cardiopulmonary parameters in 16 elite male wrestlers (W), 21 water polo player (WP) and 20 sedentary age-matched subjects (C). Plasma levels of NT-pro-BNP, cortisol and adrenocorticotropic hormone (ACTH) were measured using immunoassay sandwich technique, radioimmunoassay and radioimmunometric techniques, respectively, 10 min before test (1), at beginning (2), at maximal effort (3), at 3rd min of recovery (4). In all groups, NT-pro-BNP decreased between 1 and 2; increased from 2 to 3; and remained unchanged until 4. ACTH increased from 1 to 4, whereas cortisol increased from 1 to 3 and stayed elevated at 4. In all groups together, ΔNT-pro-BNP2/1 predicted peak oxygen consumption ($B = 37.40$, $r = 0.38$, $p = 0.007$); cortisol at 3 predicted heart rate increase between 2 and 3 ($r = -0.38$, $B = -0.06$, $p = 0.005$); cortisol at 2 predicted peak carbon-dioxide output ($B = 2.27$, $r = 0.35$, $p < 0.001$); ΔACTH3/2 predicted peak ventilatory equivalent for carbon-dioxide ($B = 0.03$, $r = 0.33$, $p = 0.003$). The relation of cortisol at 1 with NT-pro-BNP at 1 and 3 was demonstrated using logistic function in all the participants together (for 1/cortisol at 1 $B = 63.40$, 58.52; $r = 0.41$, 0.34; $p = 0.003$, 0.013, respectively). ΔNT-pro-BNP2/1 linearly correlated with ΔACTH4/3 in WP and W ($r = -0.45$, -0.48; $p = 0.04$, 0.04, respectively). These results demonstrate for the first time that HPA axis and NT-pro-BNP interface in physical stress probably contribute to integrative regulation of cardiopulmonary performance.

1. Introduction

The endocrine system plays a key role in stress situation, including physical activity, which is frequently used as a stress model [19]. Hormones have been documented to have an important role in chronic adaptation to physical stress [52]. Stress system activation implies secretion of hypothalamic corticotropin releasing hormone, which stimulates pituitary proopiomelanocortin (POMC) secretion [102]. POMC is the precursor peptide of adrenocorticotropin hormone (ACTH), which partially regulates cortisol secretion from adrenal glands [20,56]. ACTH and cortisol, besides epinephrine and norepinephrine, are the most important stress hormones [1]. During acute stress, the circadian periodicity of

Abbreviations: ACTH, adrenocorticotropic hormone; BSA, body surface area; BW, body weight; C, controls; CPET, cardiopulmonary exercise test; DBP, diastolic arterial blood pressure; FFM, fat free mass; FM, fat mass; HR, heart rate; HPA, hypothalamic–pituitary–adrenocortical; NT-pro-BNP, N-terminal fragment of brain natriuretic peptide; SBP, systolic arterial blood pressure; peakVCO2, peak carbon-dioxide output; peakVE/VCO2, peak ventilatory equivalent for carbon-dioxide; peakVO2, peak oxygen consumption; W, wrestlers; WP, water polo players.

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ACTH secretion disappears [35], thus, circulating ACTH increases in a few minutes and certain level of ACTH is a reliable measure of acute stress, unlike the cortisol, which is more a measure of chronic stress and has protective role [63,96]. However, the activation of stress system exhibits marked variability [72], depending on age [34], gender, race, genetic factors [11], nutrition [7], psychological factors [54,83], type of stress and physical activity [2,17]. There are numerous reports showing the relationship between physical stress and hypothalamo–pituitary–adrenal (HPA) axis, which deals mostly with the influence of physical activity to stress hormones levels [2,17,19,21,44,67,98,101]. It was shown that higher level of physical activity is associated with lower HPA axis reactivity to psychosocial stress [61,80]. A growing body of evidence suggest that remaining physically active is beneficial for those undergoing chronic stress of another kind [50,77,81]. These relationships are likely mediated at least partially trough repeated and prolonged activation of HPA axis [77]. On the other hand, it was shown that greater diurnal decline of the HPA axis is associated with better physical performance in later life [33]. The regulatory mechanisms for the complex relation of physical stress and HPA axis, together with the differential responses of HPA axis to different type of stress, are predicted to be at the adrenal level and stress regulatory brain areas [5,22]. This theory is supported by morphological and biochemical changes in adrenal cortex and medulla due to exercise [8]. However, biological effects of stress hormones are still not completely elucidated, although their role in complex interrelation of endocrine, metabolic, immune, neurological and cardiovascular system in stress situations is based on assumption [95]. To achieve complex regulatory role, HPA axis interacts with hypothalamo–pituitary–thyroid axis, hypothalamo–pituitary–gonad axis, hypothalamo–pituitary–growth hormone axis [48,60], brain serotonergic, noradrenergic and dopaminergic systems [72] and renin–angiotensin–aldosterone system [9,31]. In addition, putative role of several peptides in these complex regulations and interaction is under investigation. For example, physical activity elicits region specific changes in CART expression in the adrenal gland and stress regulatory brain areas, thereby indicating that CART fragments may have a role in the regulation of the HPA and sympatho–adrenal axis activity during physical stress [5]. Cardiac hormone BNP was first identified in the adrenal medulla of rats as an aldosterone secretion inhibitory factor [68], but there are number of reports showing the regulatory effects of BNP on ACTH and cortisol secretion in several mammal species [40,66,75]. Furthermore, in humans NT-pro-BNP is implicated in the regulation of HPA responses to psychological stressors [4], suggesting interreaction of these hormonal systems in adaptation to stress. However, the pathways of HPA axis activation are different in physical and emotional stress, leaving the relation of NT-pro-BNP and HPA axis during physical stress unclear [43]. Furthermore, as NT-pro-BNP is well known marker of global cardiac function, and has predictive value for cardiopulmonary parameters, which we have partially shown in our recent paper [74], it is possible that HPA axis in coordination with NT-pro-BNP take a part in the regulation of cardiopulmonary function during stress. Therefore, the aim of this study was to further elucidate the HPA axis activation during acute physical stress in different chronic physical stress models and its interface with NT-pro-BNP, as well as their predictive value for cardiopulmonary performance.

2. Materials and methods

2.1. Participants

Participants in this study were 57 male subjects matched for age (21 elite water-polo players, 16 elite wrestlers and 20 sedentary subjects). Athletes have trained intensively for more than 10 years and all have been successfully competitive at the international level for the past 5 years. Most of water polo players were the members of the national team and all of wrestlers won medals at the international level. Both groups of athletes performed combined strength and endurance training protocols. Wrestlers were in a period of preparations for the international competition at the time they were examined. They had 9 h of wrestling a week, 4 h of power training in the gym so as to improve the explosive strength and 4 h of high intensity running a week (4 km per training, at heart rate 85–100% of maximal). Water polo players were also in a period of preparations for the competition. They trained 12 h a week in the pool, with at least 2 km of swimming per each training, and three additional hours a week in the gym where they performed both power and endurance exercises. Control subjects were not engaged in sporting activities other than at recreational level (lesser then 2 h a week for the last 10 years). Also, a detailed personal and family history of illness were obtained from all participants, and thereafter they embarked on physical examination, blood tests and ECG recording. Though some of them had limb injuries in their personal history, they declared any diseases and risk factors (hypertrophic cardiomyopathy, hypertension, arrhythmias, diabetes, renal diseases, cardiac and other infections, smoking, anabolic steroids usage, etc.), which were the exclusion criteria because of the influence on myocardial function and total functional capacity of the body. There was no record of any chest pain and loss of conciousness. Thus, physical examination and blood tests showed that all of them were healthy and normotensive. ECG was physiological. In addition, there was no family history of hypertrophic cardiomyopathy and sudden cardiac death. The participants underwent the study after they have been given an informed consent and finally, the study was approved by the Local Ethical Committee.

2.2. Anthropometry

Body weight, fat mass (FM) and fat free mass (FFM) were obtained by bioelectrical impedance analysis using Tanita weight (phase sensitive multi-frequency analyzer Data Input GmbH 2000, using software Nutri 3). Body surface area (BSA) was calculated according to the DuBois and DuBois formula [23].

2.3. Ergospirometry

All the athletes underwent a progressive continuous cardiopulmonary exercise test on treadmill based on breath by breath method to assess peak oxygen consumption (peakVO2), as the measure of the functional capacity, peak carbon-dioxide output (peakVCO2), maximal heart rate (HRmax) and peak ventilatory equivalent for carbon-dioxide (peakVE/VCO2), which was obtained as the ratio of peak minute ventilation (peakVE) and peakVCO2. The protocol involved 3 min rest, 2 min at speed 6 km/h and 2% inclination, 2 min at speed 9 km/h and 2% inclination, with an increase of inclination for 2% every 2 min after, until the criteria for maximal test were reached, and 3 min recovery. The protocol was made by pretesting nine randomly chosen subjects to optimize the duration of the test (8–12 min) as recommended. The testing of all subjects was performed at the same time of the day [39,103].

2.4. Blood analysis

Examiners were free of food and drink (except water) at least 3 h before collecting blood samples. In order to avoid hormonal stimulation by needle punctuation, all blood samples were taken from braunii which was placed into the patient's brachial vein before the test. Blood was taken in four phases of the test as follows: 20 ml at rest, 10 min before CPET (phase 1); 20 ml at