



Short-term exercise combined with Acipimox administration induces an increase in plasma ACTH and its subsequent fall in the recovery phase in bulimic women

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ABSTRACT

Objective: Free fatty acids (FFA)-adrenocorticotropin (ACTH) feedback loop between adipose tissue and the hypothalamic-pituitary centers in the brain has been suggested to be affected by the exercise and by administration of anti-lipolytic drugs. Also leptin may be affected by exercise. Dysfunction of FFA-leptin-ACTH secretion might be involved in binge eating and subsequent purging as is the case in bulimia nervosa (BN).

Methods: In the present single-blind, randomized study, we explored responses of plasma ACTH, leptin and FFA concentrations to exercise (45 min, 2 W/kg of lean body mass [LBM]) with Acipimox (Aci), an anti-lipolytic nicotinic acid analog, or placebo randomly received in nine women with BN and nine healthy women.

Results: The exercise with Aci administration resulted in plasma ACTH ($p < 0.001$) and leptin increase higher in BN patients and a decrease in the plasma FFA levels in both groups. The falling of plasma ACTH ($p < 0.01$) levels in the post-exercise recovering phase (90-minute) with Aci administration is more expressed in BN patients. The exercise induced an increase in plasma ACTH ($p < 0.05$) and FFA levels and a decrease in the plasma leptin level in both groups.

Conclusions: We demonstrated that the Aci-induced elevation in plasma ACTH ($p < 0.001$) levels after the exercise higher in BN patients and that the falling of plasma ACTH ($p < 0.01$) levels in the post-exercise recovering phase (90-minute) with Aci administration is suppressed only in BN patients, while Aci increased plasma leptin levels in this recovering phase more in BN patients. Therefore, these observations led us to suggesting that FFA-leptin-ACTH are involved in the dysregulation of neuroendocrine profile in this syndrome and that Aci affects a FFA-independent mechanism. In conclusion, Aci can be considered acceptable in the treatment of eating disorders, and it may also serve as an alternative low-dose dexamethasone suppression test (LDDST) in these patients.

Trial registration: Australia and New Zealand Clinical Trials Register (ANZCTR): ACTRN12612000309886.

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1. Introduction

Free fatty acids (FFA) have been shown to inhibit both the hypothalamic and anterior pituitary functions in humans and other animals [1,2]. Recent studies in humans [1,3] demonstrated that the increase in plasma FFA levels induces a decrease in basal and exercise-induced plasma adrenocorticotropin (ACTH) secretion,

suggesting that there may be an inhibitory feedback link between plasma FFA levels and the hypothalamic-pituitary centers in the brain.

Patients with anorexia nervosa (AN) and bulimia nervosa (BN) are often stressed and anxious. Thus, chronic exposure to various stressors leads to increased hypothalamic corticotropin-releasing hormone (CRH) drive [4,5]. However, AN patients are associated with unchanged plasma ACTH levels and normal or elevated fasting plasma FFA levels [6]. Likewise, BN patients exhibit normal or increased plasma ACTH levels [5,7]. Despite having higher plasma ACTH, acute bulimic patients showed a blunted response of ACTH to CRH [5] though exaggerated rather than blunted ACTH response would be expected in this syndrome [8]. This indicates that the ACTH secretagogue activity in BN with unchanged fasting plasma FFA levels is so far poorly understood.

Recently, Lanfranco et al. [9] reported in AN higher ACTH sensitivity to the inhibitory effect of intravenous FFA load than in the controls. Furthermore, in obese women Kok et al. [10] observed that lowering of plasma FFA levels by Acipimox (Aci) reduced ACTH release. Interestingly, there was no correlation between the reduction

Abbreviations: ACTH, adrenocorticotropin; NPY, neuropeptide Y; FFA, free fatty acids; CRH, corticotropin-releasing hormone; AVP, arginine-vasopressin; GH, growth hormone; BN, bulimia nervosa; AN, anorexia nervosa; C, controls; Aci, Acipimox; HPA, hypothalamic-pituitary-adrenal; BMI, body mass index; % BF, percentage of body fat; LBM, lean body mass; ECG, electrocardiogram; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; SNS, sympathetic nervous system; LDDST, low-dose dexamethasone suppression test; MRI, magnetic resonance imaging; ns, not significant; n, number of subjects; p.o., per os.

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of plasma FFA levels and the decrease of ACTH production after Aci treatment in the obese women.

CRH is known to be a key hypothalamic factor in ACTH secretion but not during short-term exercise in humans. Physical exercise stimulates the ACTH production through a second ACTH secretagogue, such as arginine-vasopressin (AVP) activation [1]. Furthermore, alterations in secretion of AVP have been reported in AN and BN. Interestingly, in an inactive and an active phase of BN disease there may be a chronic imbalance between stimulation and inhibition of CRH secretion involving AVP and CRH neurons [11,12].

In our recent report, we demonstrated a higher response of plasma neuropeptide Y (NPY) to Aci during exercise in patients with BN, and also confirmed that NPY is one of the primary systems regulating the stress response that is relevant to BN and AN [13]. Intriguingly, it is possible that NPY contributes to both binge eating and subsequent purging in BN patients because a large intravenous bolus dose of NPY itself has been demonstrated to induce an emetic response [14].

Anti-lipolytic hormones, such as the above-mentioned NPY [15,16], ghrelin [17,18] and insulin in pharmacological doses [19] have been shown to increase plasma ACTH levels. Fruehwald-Schultes et al. [19] reported that supraphysiological hyperinsulinemia acutely stimulates ACTH secretion during euglycemia in humans. Moreover, hypoglycemia during hyperinsulinemia [20] is a well-known stimulus of ACTH secretion. However, leptin was found to dampen the hypothalamic-pituitary-adrenal (HPA) axis response to many kinds of stress and to modulate CRH and ACTH secretion in humans [21]. Furthermore, a fall of plasma leptin levels and the rise of plasma ghrelin levels induced by starvation stimulate the HPA axis with abnormal CRH and ACTH activity in AN and BN patients [4,11,12] (Fig. 1).

It has been shown that activation of the sympathetic nervous system (SNS) during exercise increases plasma FFA levels and decreases leptin production in adipose tissue whereas sympathetic blockade or Aci administration increases plasma leptin levels in humans [22,23].

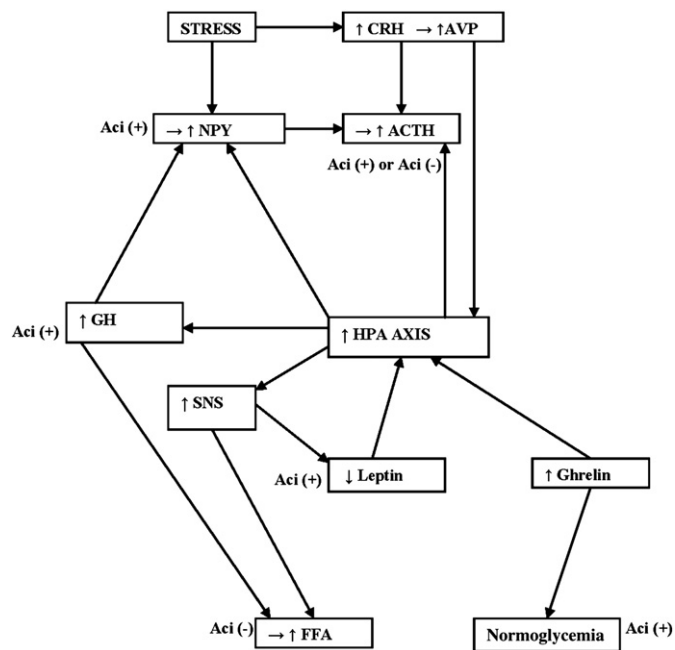


Fig. 1. Summary of the most relevant changes of the neurochemistry seen in bulimic nervosa (BN) and anorexia nervosa (AN) patients and how Acipimox (Aci) administration affects them. CRH, corticotropin-releasing hormone; AVP, arginine-vasopressin; ACTH, adrenocorticotropin; NPY, neuropeptide Y; GH, growth hormone; HPA, hypothalamic-pituitary adrenal; SNS, sympathetic nervous system; FFA, free fatty acids; Aci, Acipimox. ↑ = higher than controls, ↓ = lower than healthy controls, → = not different from healthy controls. Aci (+) = the stimulatory effect of Aci on plasma hormones and metabolites, Aci (-) = the inhibitory effect of Aci on plasma hormones and metabolites.

Very recently, it has been documented that various stressors are able to stimulate production of catecholamines in adipocytes [24]. Also leptin expression in isolated rat adipocytes was stimulated by Aci [25]. These results strongly indicate that FFA may play a role in regulating leptin secretion.

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [26] criteria for BN are recurrent episodes of binge eating and inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics or excessive physical exercise. The binge eating and inappropriate behavior both occur at least twice a week for 3 months. The most obvious sign of AN is being underweight and the DSM-IV criteria specify that the person's weight is less than 85% of what would be normal for person's age and height. The obvious signs of AN are intense fear of gaining and anorectic women suffering from it significantly misinterpret their body weight and shape, and amenorrhea.

Therefore, the initial aim of the study was to examine either the effects of administration of anti-lipolytic drug Aci or placebo during short-term exercise on plasma ACTH, leptin, insulin, blood glucose and FFA levels in BN patients and healthy women. The secondary aim was to find whether FFA are involved in exercise-induced ACTH and leptin release in BN and the controls.

2. Materials and methods

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Endocrinology in Prague. Each participant signed an informed consent form before entering the study. The study is registered at Anzctr.org.au, ACTR Number: ACTRN12612000309886.

2.1. Patients and healthy women

Nine women with BN (means ± SEM, age: 24.65 ± 1.16 years body mass index [BMI]: 20.41 ± 0.62 kg/m²; percentage of body fat [% BF]: 23.74 ± 1.71) and nine healthy women (age: 25.35 ± 0.98 years BMI: 20.8 ± 0.25 kg/m²; % BF: 24.8 ± 0.32) were recruited for this study. All subjects included in the study were nonsmokers, had no allergies and had been free of medications for at least two weeks prior to the study. Healthy volunteers had no history of cardiovascular disease, eating disorders or other psychiatric diseases. All healthy women were in the first two weeks of the follicular phase of their menstrual cycle. Patients with BN were diagnosed according to the 4th edition of the DSM-IV (American Psychiatric Association, 2000) [26]. All BN patients were clinically stable and in relatively good health, except for their eating disorder. During the period of investigation 3 bulimic patients had amenorrhea and 2 bulimic subjects had oligomenorrhea, and 4 BN patients were in the early follicular phase of the menstrual cycle. In BN patients, the average frequency of binge-purging episodes was 2.5 times per day and the average duration of their eating disorder was 6 years and 9 months. They were investigated after 1 week of hospitalization at the Department of Psychiatry of the Charles University, Prague. Other exclusion criteria were: hypertension, abnormal blood tests with significant hyperlipidemia, and history or presence of hepatic or renal disorders. For two weeks before the study they had to refrain from taking anti-depressant and contraceptive drugs. Five days before the study they had to refrain from taking aspirin, anti-histamine drugs and Tylenol (acetaminophen). Two days before the study they had to avoid the consumption of nonherb tea, coffee (even decaffeinated), alcohol, chocolate, cocoa, nuts, bananas and avoid smoking. All subjects starved overnight with the exception of drinking water. From all bulimic patients (15) and healthy women (12), 9 BN patients and 9 healthy women were acceptable during the inclusion procedure (the recruitment phase) for being randomized, i.e. 2 BN patients were excluded, 3 BN patients did not meet inclusion criteria, 1 BN patient declined to participate in the study, 2 healthy women did not meet the criteria and 1

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