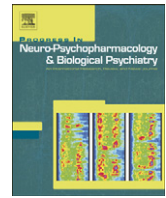




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## The role of leptin and cortisol in hyperactivity in patients with acute and weight-recovered anorexia nervosa

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### ABSTRACT

**Introduction:** In food-restricted rats, leptin as well as corticotropin releasing factor attenuate semistarvation-induced hyperactivity (SIH). Results from studies in patients with anorexia nervosa (AN) showed an association between excessive physical activity (PA) and leptin. One recent report suggests a role for cortisol in PA. In this study, we assessed the relationships between PA and both, cortisol and leptin levels at the same time in patients with acute anorexia nervosa (acAN) in comparison to recovered patients (recAN).

**Methods:** Plasma leptin, plasma cortisol, body mass index (BMI), and expert-ratings of qualities of PA were assessed in 36 acAN patients, 27 recAN patients and 44 healthy control woman (HCW). Regression analyses were used to predict PA using BMI, leptin and cortisol levels as predictor variables.

**Results:** Leptin levels but not cortisol significantly contributed to the prediction of PA in acAN. In recAN PA was not elevated and not related to endocrine parameters but correlated positively with core eating disorder symptoms.

**Conclusions:** Our work lends support to the proposed inverse association between peripheral leptin levels and excessive physical activity in AN. This relationship is specific to the state of semistarvation. The role of additional mediators remains to be clarified.

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### 1. Introduction

Elevated levels of physical activity have consistently been reported in patients with anorexia nervosa (AN) (Casper, 2006). Many investigators view this phenomenon as a core clinical symptom of AN (Casper, 1998; Hebebrand et al., 2004) and have used different terms to describe it, such as excessive or compulsive exercise, intense athleticism, an exaggerated need for physical activity, paradoxical

liveliness, hyperactivity, overactivity, motor restlessness or diffuse restlessness (Hebebrand et al., 2003). ‘Anorexia-based activity’ or ‘semi-starvation-induced hyperactivity (SIH)’ is viewed as an animal model of AN (Hebebrand et al., 2003). In essence, rats with access to a running wheel develop hyperactivity upon food restriction. Running wheel activity levels increase by 300–500% within a few days after the onset of caloric restriction. If the experiment is not terminated, rats virtually run themselves to death. SIH is more pronounced in female and young rats (Hebebrand et al., 2003). Subcutaneous leptin application was able to prevent and even reverse SIH (Exner et al., 2000; Hillebrand et al., 2005a).

Leptin is a 16-kDa protein product of the *ob* gene which is primarily secreted by adipocytes (Zhang et al., 1994). Its main physiological role is to communicate the abundance of available energy stores to the central nervous system (CNS) and to decrease food intake (Elmquist et al., 1999; Zhang et al., 2005). Consequently, the complete absence of leptin leads to increased food intake and morbid obesity (Montague et al., 1997). Plasma leptin is generally proportional to the body mass index (BMI) and underweight subjects or patients with AN show suppressed leptin levels (Hebebrand et al., 2007). There is some

**Abbreviations:** AN, anorexia nervosa; acAN, acute anorexia nervosa; BD, body dissatisfaction; BMI, body mass index; CNS, central nervous system; B, Bulimia; CRF, corticotropin releasing factor; DT, drive for thinness; EDI-2, Eating Disorders Inventory; HCW, healthy female control subjects; HPA, hypothalamic-pituitary-adrenal; PA, physical activity; recAN, recovered anorexia nervosa; SIH, semi-starvation-induced hyperactivity; SIAB-EX, Structured Interview of Anorexia Nervosa and Bulimic Syndromes; SCL-90-R, Symptom Checklist 90 Revised.

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evidence from clinical studies that motor restlessness in underweight patients with AN is connected to hypoleptinaemia (Holtkamp et al., 2006; Holtkamp et al., 2003; van Elburg et al., 2007a,b).

Others have suggested a link between hypothalamic-pituitary-adrenal (HPA) axis over-activity and physical activity. Cortisol is elevated in both underweight patients with AN (Lo Sauro et al., 2008) and semistarved running rats (Burden et al., 1993). Administration of a corticotropin releasing factor (CRF) antagonist attenuates or prevents the development of SIH (Kawaguchi et al., 2005; Rivest and Richard, 1990). Further, adrenalectomy prevents the development of SIH (Hebebrand et al., 2003); a plausible pathway for mediation of SIH is thus the hypothalamic-pituitary-adrenal axis. In agreement with this hypothesis, in one study hypercortisolism was related to hyperactivity in underweight AN patients (Klein et al., 2007).

To date, the relationships between physical activity and both cortisol and leptin levels have not been investigated conjointly in one study. We hypothesised that each parameter, cortisol as well as leptin, would explain part of the variance in physical activity among acutely underweight AN patients. In addition, we aimed to scrutinize the same relationships in long-term weight recovered AN patients and explore the association between leptin and physical activity in healthy control woman.

## 2. Methods

### 2.1. Patient population

The sample population consisted of female patients with acute AN, recovered AN and healthy control woman. Thirty-six subjects (14–29 years old) with acute anorexia nervosa (acAN) according to DSM-IV (28 of the restrictive subtype and 8 of the binge-eating/purging subtype) were admitted to eating disorder programs of an university child and adolescent psychiatry and psychosomatic medicine department.

We also included 27 female subjects (15–29 years old), who were previously treated for AN and had successfully recovered from their illness (recAN). To be considered “recovered”, subjects had to 1) maintain a BMI > 18.5 (if older than 18 years) or a BMI > 10th BMI percentile (if younger than 18 years, (Kromeyer-Hauschild et al., 2001)) for at least three months prior to the study, 2) menstruate and 3) have not binged, purged, or engaged in significant restrictive eating patterns for at least three months before venipuncture. The majority of the recAN patients ( $n = 18$ ; 66.7%) had been recovered for more than 12 months while some ( $n = 9$ ; 33.3%) had been recovered for at least 3 months but not more than 12 months.

The control group consisted of 44 normal-weight, eumenorrheic, healthy female control subjects (HCW, 14–26 years old), who were recruited through advertisement among middle school, high school and university students.

Exclusion criteria and possible confounding variables were identified using a semistructured research interview, the SIAB-EX interview (see below) and by physical examination. Comorbid psychiatric diagnoses other than eating disorders were derived from medical records. HCW were excluded if they had any history of psychiatric illness. Patients were excluded if they had a lifetime history of any of the following clinical diagnoses: organic brain syndrome, schizophrenia, substance dependence, bipolar illness, bulimia nervosa or binge eating disorder. Further exclusion criteria for all participants were: IQ less than 85, current inflammatory, neurological or metabolic illness, chronic bowel diseases, cancer, clinically significant anaemia, pregnancy, breast feeding, current use of aspirin, cortisone, antibiotics, antihypertensive medication and use of psychotropic medications or substances within the past 6 weeks.

This study was approved by the Institutional Review Board, and all subjects (and if underage their guardians) gave written informed consent.

### 2.2. Clinical measures

Current and/or past eating disorder symptoms were assessed in acAN patients within the first week of treatment and in recAN and HCW at the day of venipuncture using the expert form of the Structured Interview of Anorexia Nervosa and Bulimic Syndromes (SIAB-EX (Fichter and Quadflieg, 1999)). The SIAB-EX for subjects aged between 12 and 65 years is a semi-structured interview that assesses the prevalence and severity of specific eating-related psychopathology over the past three months according to DSM-IV diagnostic criteria. It also provides diagnoses of eating disorders according to ICD-10 and DSM-IV. Internal consistency was good and the interrater reliability ranged from .86 to .96 (Fichter and Quadflieg, 2001). Interviews were conducted by clinically experienced and trained research assistants under the supervision of an attending child and adolescent psychiatrist.

The frequency and intensity of physical activity (PA) within the 3 months before inclusion into our study was assessed using the corresponding module of the SIAB-EX as described previously (Holtkamp et al., 2003). PA was rated as being equivalent to one of five levels: First level: no excessive PA; Second level: slight and/or rare excessive PA: a person rarely exercises (for example, on weekends or in the evenings) to burn calories or to reduce weight, but can just as well turn to other activities, if they are interesting or appear more important; Third level: marked and/or occasional excessive PA: a person exercises sometimes (up to twice weekly) or with marked vigor, the person may report discomfort when prevented from PA, and distraction is possible but is associated with some discomfort; Fourth level: strong and/or frequent excessive PA: the person objectively exercises very much (every day for >1 h or three to four times a week for 2 h or more), and also experiences discomfort when prevented from PA; Fifth level: very strong excessive PA: excessive PA occurs more than once a day or for longer periods (>1.5 h/day), and the PA occurs irrespective of physical weakness and pain.

Inner restlessness or nervousness was disregarded. In accordance with the SIAB-EX manual additional information from other sources, such as nurses and therapists, were integrated with the interviewer's observations and the subject's response.

Eating disorder-specific psychopathology was assessed with the short version of the Eating Disorders Inventory (EDI-2), a self report questionnaire comprising 8 subscales (Rathner and Waldherr, 1997). Response categories range from 1 ‘never’ to 6 ‘always’. The three core subscales “drive for thinness” (DT), “body dissatisfaction” (BD) and “bulimia” (B) were part of the confirmatory analyses in this study.

General levels of psychopathology were determined using the Symptom Checklist 90 Revised (SCL-90-R) (Franke, 2002).

### 2.3. Blood collection and biochemical assessments

Within the first days of treatment initiation venous blood samples of 9 ml were collected into vacutainer tubes containing EDTA between 7:30 and 9:30 am after the subjects had fasted overnight. RecAN patients and HCW were asked to fast overnight and come to our department for a scheduled venipuncture between 7:30 and 9:30 am. After centrifugation of the blood at  $250 \times g$  plasma samples were frozen and stored at  $-80^\circ\text{C}$ . Leptin concentrations were measured by Enzyme Linked Immunosorbent Assay with a commercial kit (Human Leptin “Dual Range” ELISA, Millipore, Billerica, MA, USA) according to the manufacturer's instructions. Depending on the dilution factor specified in the protocol sensitivity was .125–20 ng/ml or .5–100 ng/ml. Cortisol concentrations were determined using the GammaCoat Cortisol RIA-Kit (Dia Sorin GmbH, Dietzenbach, Germany) according to the instructions of the manufacturer. Analytical sensitivity of the test was 5.8 nmol/l. Reference values for morning cortisol levels using this RIA are 193–690 nmol/l. Data on plasma cortisol were only available for AN patients.

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