Journal of Psychosomatic Research 78 (2015) 260–267

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Blunted neuroendocrine stress reactivity in young women with eating disorders

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ARTICLE INFO

Article history:
Received 23 April 2014
Received in revised form 20 October 2014
Accepted 4 November 2014

Keywords:
Anorexia nervosa
Bulimia nervosa
Cortisol
Hypothalamus–pituitary–adrenal (HPA) axis
Stress
Sympathetic nervous system (SNS)

ABSTRACT

Objective: Stress is known to influence risk and progression of eating disorders (EDs). However, studies investigating physiological and psychological stress responses under laboratory conditions in patients with Anorexia nervosa or Bulimia nervosa are scarce and often produce conflicting findings. We therefore aimed to compare the neuroendocrine and affective stress response in ED inpatients and healthy controls.
Methods: Twenty-eight female inpatients with Anorexia or Bulimia nervosa and 26 healthy women were exposed to the Trier Social Stress Test (TSST). Salivary cortisol and alpha-amylase (sAA) levels were assessed before as well as repeatedly after stress exposure, while heart rate and heart rate variability were determined before and during the TSST. Negative affective state was assessed at baseline and post-TSST.
Results: Compared to healthy controls, ED patients showed blunted cortisol stress responses combined with overall attenuated sAA levels. The latter was reflected in generally enhanced parasympathetic activity indicated by lower heart rate and stronger high-frequency heart rate variability throughout the TSST. Although patients reported more negative affect overall, they did not differ in their affective stress response.
Conclusions: In summary, patients suffering from eating disorders show a blunted HPA axis reactivity to stress exposure and a generally reduced sympathetic/exaggerated parasympathetic nervous system activity. This combination may contribute to elevated health risks seen in eating disorder patients, such as enhanced inflammatory activity, and thus provide insight into the underlying stress-related mechanisms.

Introduction

Eating disorder (ED) related behaviors like keeping a diet, the desire to be thinner or performing compensatory behavior such as self-induced vomiting or excessive sport frequently occur among young women [1–3]. However, only a small number of these women develop an eating disorder like Anorexia nervosa (AN) or Bulimia nervosa (BN; [4]). The etiology of these disorders is still relatively unknown [5]. Stress has been identified as a potential risk factor for the development of eating disorders [6], since there is evidence that patients often experience severe life events or chronic stress before the onset of the ED [7]. Although chronic stress is not specific to patients with EDs [6], this finding might indicate that there is a strong activation of stress mediating physiological systems before the onset of an ED. This is in line with current stress–disease models suggesting that chronic stress or an inadequate stress response facilitates emotional disorders [8–11].

The two prominent physiological systems that mediate the stress response are the sympathetic nervous system (SNS) and the hypothalamus–pituitary–adrenal axis (HPAA; [12]). The former system belongs to the autonomic nervous system and allows short-term adaptation to challenging conditions within a few seconds through the release of epinephrine and norepinephrine from the adrenal medulla as well as through direct innervation of target tissues. The latter system complements the former through the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids (GCs), mainly cortisol in humans [13]. Cortisol permeates the blood–brain barrier and activates central corticosteroid receptors, thereby regulating its own release [12,14].

Besides acute cortisol increases indicating HPAA reactivity, cortisol also shows a circadian rhythm indicating basal HPAA activity [15]. This rhythm is characterized by a cortisol awakening response (CAR)

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http://dx.doi.org/10.1016/j.jpsychores.2014.11.001
0022-3999/

associated with 50–100% increase in cortisol over the first 30–45 min after awakening followed by a steady decline over the course of the day and a nadir in the first half of the night [16]. The CAR is significantly related to various psychosocial factors, chronic stress, health and physical conditions [17–20].

Past research on patients with EDs showed a relatively consistent pattern in terms of SNS and HPAA activity under resting conditions. In contrast to healthy controls (HC), patients with AN or BN show a blunted activity of the SNS as indicated by heart rate frequency (HRF; [21,22]), blood pressure [23,24], heart rate variability (HRV; [25]), salivary alpha-amylase (sAA; [26]), and serum norepinephrine [21,22] level. Furthermore, ED patients often display an enhanced HPAA activity with higher concentrations of CRH in cerebrospinal fluid [27] and cortisol in serum or saliva [28–31]. In terms of CAR, only one study investigated this HPAA activity marker in AN patients and found it to be enhanced compared to HC [26]. These changes were often attributed to (at least intermitted) starvation [32,33] but could be interpreted as a predisposing condition which preceded the development of an ED and make individuals more vulnerable for EDs as well [22,24].

The patterns become less consistent when looking at stress system reactivity instead of activity. While patients with AN or BN typically show a blunted SNS response to acute laboratory stressors compared to HC [21,22,30,31,34], the findings on HPAA activity are more heterogeneous. For example, in one study [31], no group differences were found between ED patients and HC in the cortisol response to a mirror exposure task. Contrarily, Zonnevylle-Bender et al. [34] and Ginty et al. [35] reported a blunted stress response to the Trier Social Stress Test (TSST; [36]) and to a ten minute mental arithmetic stress task in patients with AN and BN. Another study reported elevated cortisol levels in women with AN throughout the investigation period when compared to women with BN and HC [30]. In this study the TSST was used as well. These conflicting results may in part be due to methodological issues. Several of the studies used stress induction methods that activate the SNS but may not be very effective in eliciting a HPAA response [37]. For instance, studies used a modified Stroop color word test [38,39], an imagination task [40,41], a mental challenge task [21,24], an auditory stimulation test [42], speech tasks [43,44] or pain-induction [23]. Additionally, often rather small sample sizes were investigated. The aim of the present study was thus to investigate differences in physiological and psychological stress responses between ED patients and HC using a larger sample size and the TSST as an effective laboratory stress induction protocol [37]. Therefore the SNS, HPAA and the affective stress responses were assessed and analyzed. We expected differences in the HPAA stress response and the CAR between ED patients and HC and a lower SNS stress response and a stronger negative affect after the TSST in ED patients compared to HC. The latter prediction was based on a recent study showing that stress exposure resulted in stronger sadness responses as well as insecurity in ED patients compared to HC [45].

Importantly, for the purpose of the current study, patients with AN and BN were investigated as one group according to the transdiagnostic perspective [46,47]. This conceptualization is based on the longitudinal observation that patients with AN, BN and atypical eating disorders (AED; eating disorders of clinical severity that do not meet the criteria for AN or BN) share a core psychopathology characterized by over-evaluation and control of eating, shape and weight [47]. This is expressed in similar attitudes and behaviors, such as rigid restriction of food intake, vomiting, and over-exercise. However, the balance of under- and over-eating differs between the groups resulting in differences in body weight. Indeed, patients who do not recover from AN frequently cross-over to BN (1/4 of patients with BN had AN in the past) or AED [48–50]. Moreover, BN typically starts as AN or an AED and a particularly common outcome of BN is a chronic AED. In summary, AN, BN and AED are states on a psychopathology continuum with patients moving between these diagnostic states [51–53].

Methods

Participants

A total of $N = 54$ women were recruited. Prior to testing, participants underwent a diagnostic examination using the German versions of the *Structured Clinical Interview for Axis I of the DSM-IV* (SCID-I; [54]), the *Beck-Depression-Inventory* (BDI; [55]), the *Symptom-Checklist-90-Revised* (SCL90-R; [56]) and the *Eating Disorder Examination-Questionnaire* (EDE-Q; [57]). The SCID was administered by trained professionals with at least one year experience in the use of this diagnostic instrument. Twenty-eight inpatients with ED participated during the first week of their treatment. Of those, $n = 18$ fulfilled the diagnostical criteria of the text revised 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, [58]) of AN and $n = 10$ patients those of BN. All patients were consecutive patients and were asked for participation to the study directly on the first or the second day after admission to the clinic. They were medication-free (except of oral contraceptives) and were combined into one group according to the transdiagnostic theory of EDs [47]. Due to well-known changes in HPAA activity in post-traumatic stress disorder, borderline personality disorder or schizophrenia [59,60], patients with EDs fulfilling the criteria of at least one of those diagnoses were excluded. Duration of illness was not restricted but considered in subsequent analyses. To ensure comparability, ambulant patients were excluded as well. All patients were recruited from the Christoph-Dornier Clinic for Psychotherapy, Münster (Germany) and the Department of Psychosomatic Medicine and Psychotherapy, LWL-University Clinic, Bochum (Germany), both are specialized in the treatment of EDs. The group of HC was composed of $n = 26$ physically and mentally healthy, medication-free (except of oral contraceptives) and drug-free female students with a body mass index (BMI) within the normal range (18.5–26 kg/m^2) recruited at the University of Bochum and Münster via advertisements at the bulletin boards. Participants with previous TSST exposure and participants who did not refrain from physical exercise or eating 1 h before testing were excluded. Since ED patients often use oral contraceptives and/or smoke, we did not exclude women who smoked and/or used oral contraceptives. However, due to potential effects on HPAA reactivity [61], frequencies of both behaviors were assessed and statistically controlled. All participants provided written informed consent. The study protocol was approved by the institutional review board of the Ruhr-University of Bochum.

Trier social stress test (TSST)

The TSST was performed as described by Kirschbaum et al. [36]. In short, participants were told to introduce themselves to a committee and to convince the committee that they were the perfect applicant for a vacant position in their 'dream job'. After a five minute preparation period, each participant had to talk about her job-relevant personality traits for a duration of 5 min. If the participant finished her speech in less than 5 min, standardized questions were used. During the subsequent 5 min, the participants were asked to count backwards in steps of 17 from 2043 as fast and as accurately as possible. Whenever the participant made a mistake, she had to start over at 2043. Both members of the committee were dressed in white lab coats and acted in a reserved manner. The TSST has been shown to be highly effective in eliciting a HPAA response [37], a SNS response, and a negative affect state [62].

Saliva sampling and biochemical analyses

Saliva samples were obtained using the Salivette sampling device (Sarstedt, Nümbrecht, Germany) to assess free cortisol and sAA levels as HPAA and SNS markers, respectively [63,64]. To assess stress system reactivity, saliva samples were collected 1 min before (−1) and 1 (+1), 10 (+10) and 25 (+25) min after the TSST. To assess the CAR (basal