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Increased psychological and attenuated cortisol and alpha-amylase responses to acute psychosocial stress in female patients with borderline personality disorder

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Summary
Objective: Borderline personality disorder (BPD) is characterized by increased self-reported stress and emotional responding. Knowledge about the psychological and physiological mechanisms that underlie these experiences in BPD patients is scarce. The objective was to assess both psychological and endocrinological responses to a standardized psychosocial stressor in female BPD patients and healthy controls.
Methods: A total of 15 female BPD patients and 17 healthy control subjects were included in a case—control study. All subjects were free of any medication, had a regular menstrual cycle, and were investigated during the luteal phase of their menstrual cycle. Co-occurring current major depression, current substance abuse/dependence, and lifetime schizophrenia or bipolar I disorder were excluded. Psychological measures of stress, salivary cortisol, salivary alpha-amylase, plasma ACTH, plasma norepinephrine and epinephrine concentrations were measured before, during, and after exposure to a standardized psychosocial stress protocol.
Results: BPD patients displayed maladaptive cognitive appraisal processes regarding the upcoming stressor as well as significantly higher subjective stress, coupled with a substantial cortisol and alpha-amylase hyporeactivity to the stressor in comparison to the controls. No significant differences for ACTH and catecholaminergic responses were observed, while the ACTH:cortisol ratio was higher in BPD patients than in controls.

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Conclusions: Attenuated cortisol responsiveness in BPD patients might in part be explained by decreased adrenal responsiveness to endogenous ACTH and altered central noradrenergic activation as reflected by alpha-amylase.

1. Introduction

Borderline personality disorder (BPD) presents as a heterogeneous constellation of symptoms with dysfunctional affect regulation at its core (Lieb et al., 2004b). Several studies clearly indicate that individuals with BPD experience higher emotional reactivity, emotional intensity, and slower return to baseline of affective arousal, compared to healthy controls and individuals with other personality disorders (Koenigsberg et al., 2002; Stiglmayr et al., 2005; Ebner-Priemer et al., 2007). BPD patients are further characterized by displaying dysfunctional behavior such as non-suicidal self-injury as a strategy to regulate these intense levels of distress (Kleindienst et al., 2008). Stressful life events have been reported to accumulate under daily life conditions in adult BPD patients (Zanarini et al., 2005). Interestingly, experimental studies clearly demonstrate that central stress coping mechanisms fail within this group of patients. For instance, functional neuroimaging studies in BPD patients revealed strong evidence for alterations of the limbic circuitry including insula, hippocampus, and amygdala hyperreactivity, and alterations in frontal and prefrontal regions (Mauchnik et al., 2005). The neurochemical underpinnings of these limbic dysregulations, however, are unclear. There is general agreement that the stress hormones cortisol and corticosterone target the limbic brain affecting cognitive processes and emotional arousal (De Kloet et al., 2005). Recent evidence shows that corticosteroid hormones exert both rapid and slow non-genomic effects on neurons in the hippocampus, the amygdale, and frontal and prefrontal regions. According to De Kloet et al. (2008), corticosteroids seem to modulate a biphasic stress response: during the initial phase corticosteroids promote hippocampal excitability and amplify the effect of other stress hormones. These fast responses are complemented by slower glucocorticoid receptor mediated effects which facilitate downregulation of temporarily raised excitability and recovery from stressful experience. From this perspective, both cortisol hyper- or hypo-secretion could play a role in promoting affective dysregulation in BPD patients.

However, so far, studies examining alterations of the hypothalamic–pituitary–adrenal (HPA) axis in BPD have been scarce. It has been fairly consistently shown that dexamethasone suppression (DST) in BPD is neither particularly sensitive nor specific (Lahmeyer et al., 1988; Korzekwa et al., 1991; De la Fuente and Mendlewicz, 1996). The majority of these studies included BPD patients with comorbid major depressive disorder (MDD) or posttraumatic stress disorder (PTSD), which both are known to affect the HPA axis (Steckler et al., 1999; Yehuda, 2002). In a more naturalistic study, Lieb et al. (2004a) collected salivary cortisol during daily life conditions for 14 h after awakening. Patients with BPD displayed significantly higher salivary cortisol levels than healthy controls as demonstrated by higher total cortisol in response to awakening and higher total daily cortisol levels. However, no correlation could be found between monitored subjective levels of distress and related salivary cortisol levels.

We are aware of two published studies addressing physiological responses to experimentally induced acute stress in BPD, both showing unclear results. In one study (Simeon et al., 2007), 13 BPD patients and 11 healthy controls were exposed to the Trier Social Stress Test, a standardized psychosocial stressor (TSST; Kirschbaum et al., 1993). No difference in cortisol stress reactivity between BPD patients and healthy controls was found, but BPD patients with high levels of long-term dissociation showed elevated plasma cortisol peaks compared with low dissociation BPD patients and controls. In the second study (Walter et al., 2008), BPD patients ($n = 9$) did not show different cortisol stress reactivity levels to an interpersonal conflict task in comparison with 12 healthy controls, but displayed elevated cortisol levels during recovery. However, in both studies the samples consisted of male and female subjects and the menstrual cycle of the latter were not timed. Since this variable has a strong impact on cortisol secretion during the TSST (Kirschbaum et al., 1999), the interpretation of the data is difficult. Thus, it remains to be determined whether BPD patients display altered HPA axis stress reactivity.

The same is true for information on the autonomic nervous system (ANS) in BPD. Emotional dysregulation has been shown to correlate with imbalances in noradrenergic neurotransmission, although the findings are mixed (Gurvits et al., 2000). Ebner-Priemer et al. (2008) assessed distress and heart rates in 50 BPD patients and 50 healthy controls under 24 h daily life conditions. BPD patients reported significantly more distress and displayed elevated heart rates, but the correlation between physiological arousal and psychological distress were equal in both groups. Enhanced ANS reactivity, however, cannot be excluded, since most of the patients were on medication. The lack of sufficient studies measuring ANS parameters might in part be explained by the insufficient availability of markers that reliably reflect sympathetic activity (Grassi and Esler, 1999). With the recent suggestion of the salivary enzyme alpha-amylase being a valid and reliable marker of central sympathetic activity (Ehlert et al., 2006; Nater and Rohleder, 2009; Rohleder and Nater, 2009) it is now possible to measure both HPA axis and ANS activity in a convenient and non-invasive manner (Nierop et al., 2006).

Summarizing, there is evidence that BPD patients display insufficient cognitive and neural stress regulation, but the role of neither the HPA axis nor the ANS is sufficiently studied.

The objective of the current study was therefore to assess both psychological and neuroendocrine responses to a standardized psychosocial stressor in a female population of BPD patients and healthy subjects, controlled for known covariates. We hypothesized (1) that BPD patients experience enhanced subjective stress in face of an acute psychosocial stressor, compared to healthy controls; (2) that secretion of cortisol and ACTH in BPD is disturbed, indicating dysregulated