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Diminished cortisol responses to psychosocial stress associated with lifetime adverse events

A study among healthy young subjects

Bernet M. Elzinga^{a,*}, Karin Roelofs^a, Marieke S. Tollenaar^a,
Patricia Bakvis^{a,b}, Johannes van Pelt^c, Philip Spinhoven^a

^aDepartment of Clinical, Health and NeuroPsychology, University of Leiden, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands

^bStichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

^cDepartment of Clinical Chemistry, Leiden University Medical Center (LUMC), Leiden, The Netherlands

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Summary

Background: Animal and human studies have found that prior stressful events can result in an altered reactivity in the HPA axis. The aim of the present study was to investigate the role of adverse events in childhood on cortisol reactivity to psychosocial stress in young healthy subjects ($n = 80$).

Methods: Salivary cortisol levels were measured before, during and after exposure to a psychosocial stress task in healthy men and women with high ($n = 33$) and low ($n = 47$) exposure to adverse childhood events.

Results: A significant blunted cortisol response was found in individuals with a history of adverse events compared to individuals with no adverse life events, with no differences in baseline cortisol levels. This finding appeared to be primarily driven by men. The groups did not differ on any other physiological or subjective stress measure, including heart rate, blood pressure, and subjective tension.

Conclusions: These findings suggest that, at least in healthy young males, adverse childhood events are associated with changes in HPA-axis functioning. Longitudinal studies are needed to investigate whether the blunted cortisol response is a risk factor in the etiology of psychiatric disorders or rather reflects resiliency with regard to the development of psychopathology.

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*Corresponding author. Tel.: +31 71 5273745; fax: +31 71 5274678.

E-mail address: elzinga@fsw.leidenuniv.nl (B.M. Elzinga).

1. Introduction

Compelling evidence is accumulating that early trauma, including sexual, physical and emotional abuse, is associated with an increased risk to develop a variety of psychiatric disorders in adulthood, including posttraumatic stress disorder (PTSD), depression, dissociative disorders, alcohol and substance abuse, and borderline personality disorder (Beitchman et al., 1992; Bremner et al., 1993; Draijer and Langeland, 1999; Kendler et al., 1993; McCauley et al., 1997; Mullen et al., 1996; Stein et al., 1996). Given the fact that childhood abuse may affect as many as one in five individuals (McCauley et al., 1997), it is very important to understand the psychological and neurobiological processes underlying the increased stress vulnerability associated with childhood abuse.

In preclinical studies, there is a growing body of evidence demonstrating that early adverse events may have a lasting impact on the neurobiology of the stress response, particularly on the stress-regulating hypothalamic–pituitary–adrenal (HPA) axis (see Heim and Nemeroff, 2001; Kaufman et al., 2000; Sanchez, 2006, for reviews). The HPA axis is activated during prolonged stressful events resulting in a marked increase in the release of the stress-hormone cortisol (or corticosterone, depending on the system) from the adrenal. Cortisol release from the adrenal is regulated by the adrenocorticotropine releasing hormone (ACTH) from the pituitary, which in turn is primarily regulated by corticotropin releasing factor (CRF) from the paraventricular nucleus of the hypothalamus. The responses of the HPA axis are regulated by a complex negative feedback system, exerted by glucocorticoids.

Numerous studies in rodents and primates have shown that early life stressors, such as (prolonged) maternal separation, may result in chronic increases in plasma glucocorticoid levels and ACTH and a potentiation of glucocorticoid responsiveness to subsequent stressors in adulthood, which is primarily driven by an enhanced CRH drive (Anisman et al., 1998; Coplan et al., 1996; Ladd et al., 1996, 2000; Levine et al., 1993; Plotsky and Meaney, 1993; Plotsky et al., 2005; Sapolsky, 1997). Besides the enhanced neuroendocrine responses, prolonged early life stress in animals is also associated with enhanced anxiety, decreased social interaction, and impaired cognitive performance later in life (Kaufman et al., 2000).

Exposure to brief (intermittent) stress early in life, in contrast, has been associated with a diminished activation of the HPA axis to novel stressors later in life (Parker et al., 2004, 2006; Anisman et al., 1998; Denenberg, 1999), together with diminished anxiety and relative unimpaired cognitive functions. Neuroendocrine stress resistance in rodents is mediated, in part, by enhanced glucocorticoid-feedback sensitivity (Meaney, 2001), although evidence for this mechanism was not found in primates (Parker et al., 2006).

Taken together, these observations suggest that in animals exposure to early life stress may lead to an increase in HPA-axis reactivity to novel stressors after exposure to relatively severe or chronic stress, and to a decrease in cortisol reactivity after minor or brief stressors. The effects of stress exposure on HPA-axis functioning depend on many factors, however, including the nature, timing, frequency, duration,

and perceived intensity of the stressful events. Other factors that may moderate the outcomes of early adversity are social support (e.g., nurturing versus neglecting caregiver), gender, and genetic factors on individual variability in vulnerability (see Heim et al., 2004; Sanchez, 2006; Sanchez et al., 2001).

In humans, studies on the effects of early abuse on the reactivity of the HPA axis to stressors later in life are scarce, and have so far almost exclusively been conducted in patients with mood or anxiety disorders. Heim et al. (2000b) found that adult women with a history of childhood abuse and a current major depression (and comorbid PTSD) exhibited increased cortisol and ACTH responses to a psychosocial stress task compared to women with a current major depression and no abuse history, and to women without a psychiatric disorder either with or without an abuse history. Interestingly, peak cortisol responses were predicted by a history of childhood abuse, the number of separate abuse events, the number of daily hassles and the severity of the depression (Heim et al., 2002). Moreover, among male and female patients with PTSD related to a history of early abuse, Bremner et al. (2003) found elevated cortisol levels in anticipation and during a cognitive challenge task compared to healthy controls with no PTSD or early abuse, which appeared to be primarily driven by men. Neither a control group with a history of abuse without PTSD, nor a group with PTSD and late trauma were included in this study, however. Therefore it is not possible to disentangle the effects of PTSD symptomatology from the impact of the abuse itself on cortisol responsiveness to the cognitive challenge. Nevertheless, these studies are consistent with a model of HPA-axis sensitization after early trauma, so that subsequent exposure to stressful events may lead to increased stress responses.

Contrary findings have also been reported, however. A recent study that assessed cortisol reactivity to a physical stress task (i.e., a cold pressor task) among PTSD patients with either a history of early or late trauma found that patients with early trauma had *lower* cortisol levels both at baseline and throughout the testing period compared to PTSD patients with late trauma and to controls without PTSD or trauma history (Santa Anna et al., 2006). Lower basal cortisol levels have also been reported in rape victims with a history of childhood sexual abuse soon after the rape when compared to women without early abuse histories (Resnick et al., 1995). Moreover, the women with previous abuse were also more likely to have developed PTSD 3 months later (Yehuda et al., 1998).

Taken together, these studies suggest that among patients with a current psychiatric disorder, early sexual and/or physical trauma is related to changes in HPA-axis reactivity, of which some are suggestive of enhanced cortisol reactivity and blunted basal cortisol levels. These studies are very important in illustrating the chronic impact of adverse life events on stress reactivity in psychiatric patients. One major limitation in interpreting these findings is, however, that in most studies (except for the study of Heim et al., 2000b) the effects are confounded with current psychiatric symptoms. Hence, what remains unknown is whether changes in HPA-axis reactivity constitute a premorbid risk factor that was present before the development of the disorder, or rather are related to the current psychiatric status.

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