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Decreased cortisol awakening response after early loss experience

Gunther Meinlschmidt, Christine Heim*

Division of Clinical and Theoretical Psychobiology, Department of Psychobiology, University of Trier, 54286 Trier, Germany

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Summary Early loss experience (ELE) due to death or separation is a major risk factor for the development of several psychiatric and physical disorders in adulthood. Few studies have focused on the effects of ELE on neuroendocrine systems, which might mediate this risk in part. The goal of this study was to evaluate salivary cortisol responses to awakening in individuals with and without ELE. A total of 95 healthy college students (29 men, 66 women) completed a questionnaire on ELE and were instructed to collect saliva immediately after awakening and 30 min later. Fifty-five of the 95 subjects reported having experienced the separation or divorce of their parents and/or the death of a close relative before the age of 14 years. Subjects with such ELE exhibited decreased salivary cortisol responses to awakening compared to subjects without ELE (net increase: 4.78 nmol/l versus 9.83 nmol/l; $t_{93}=2.88$, $p=0.005$). The effect was most pronounced in individuals who experienced multiple types of ELE, while there were no sex differences. In conclusion, ELE appears to be associated with decreased salivary cortisol responses to awakening. Low cortisol awakening responses are believed to reflect altered dynamics of the hypothalamic-pituitary-adrenal (HPA) axis, possibly conferring risk for certain stress-related disorders.

1. Introduction

At the beginning of the last century, Sigmund Freud had recognized that experiences of loss early in life are linked to the later manifestation of melancholia (Freud, 1957). This seminal observation was subsequently confirmed in a large number of epidemiological, twin and case-control studies demonstrating that loss of a parent due to death or separation increases the risk for major depression in adulthood (Agid et al., 2000). Early loss experience (ELE) was also found to predispose for a variety of other psychiatric disorders, including bipolar disorder, anxiety disorders, schizophrenia, and alcohol abuse (Agid et al., 1999; Kendler et al., 1992, 2002a,b). There is also evidence for a relationship between ELE and physical illnesses, functional somatic syndromes

* Corresponding author. Address: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 2004 Ridgewood Dr, Tufts House, Suite 103, Atlanta, GA 30322, USA. Tel.: +1 404 727 5835; fax: +1 404 727 3233.
E-mail address: cmheim@emory.edu (C. Heim).

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and several health risk behaviors (Lowman et al., 1987; Felitti et al., 1998; Agid et al., 1999).

There is abundant evidence from research in rodents and non-human primates that maternal separation early in development induces persistent alterations of brain circuits involved in the mediation of stress and emotion, leading to altered neuroendocrine responsiveness and behavioral changes (Ladd et al., 2000; Sánchez et al., 2001). While maternal separation in rodents has been associated with increased stress responsiveness, findings in non-human primates exposed to maternal or social deprivation are less consistent with some studies reporting increased (Higley et al., 1991, 1992; Fahlke et al., 2000) and others reporting decreased (Clarke, 1993; Lyons et al., 1999) basal or stress-induced cortisol output. Of note, decreased cortisol excretion particularly in the early morning hours has been reported for marmoset monkeys exposed to repeated maternal separation (Dettling et al., 2002). Given the important physiological and behavioral effects of cortisol in the organism's adaptation to the environment, such changes might plausibly confer vulnerability to various pathologies, likely in the context of genetic risk.

Although there is a multitude of clinical studies documenting changes of the hypothalamic-pituitary-adrenal (HPA) axis in maltreated children and adults with childhood abuse histories (De Bellis et al., 1999; Teicher et al., 2002; Heim et al., 2004), surprisingly few studies have focused on the neuroendocrine effects of ELE. In one study, children adopted from Romania who spent more than eight months in their first years of life in an orphanage demonstrated increased salivary cortisol concentrations 15–30 min after awakening when compared to control children (Gunnar et al., 2001). In another study in children, the diurnal decline in salivary cortisol concentrations was found to be negatively correlated with out-of-home placements and the extent of emotional deprivation, suggesting elevated diurnal cortisol secretion (Kaufman, 1991). In contrast, Carlson and Earls (1997) report that severely socially deprived children show significantly lower salivary cortisol concentrations at 8 a.m. in the morning compared to home-reared children. Studies in adults have provided some evidence for HPA axis hyperactivity after ELE. Breier et al. (1988) measured increased basal cortisol levels in a single afternoon blood sample obtained from adults with early parental loss who had a history of psychopathology. Both psychopathology and cortisol concentrations were negatively associated with the quality of life and social support after the loss. Another recent study reported that adult men with ELE due to parental death exhibit increased salivary cortisol concentrations at various time points throughout the day compared to controls, when aggregating measures over 5 consecutive days. The most robust difference was detected at 8 a.m. in the morning and the effect was not due to increased depression or anxiety (Nicolson, 2004). Finally, in a study by Luecken (2000), adults with early parental loss experiences who had a poor relationship with the surviving parent, showed increased cortisol responses during a speech stressor. Interestingly, adults with other types of adversity, i.e. child abuse, also exhibit increased stress responses (Heim et al., 2000b), but cortisol levels in the morning are low (Heim et al., 2001), similar to some findings in deprived non-human primates or severely deprived children (Dettling et al., 2002; Carlson and Earls, 1997).

Importantly, with the exception of the study by Gunnar et al. (2001), the above studies reporting either increased or decreased early morning cortisol levels in ELE collected samples at fixed time points, e.g. at 8 a.m., and did not consider potential effects of different times of awakening on the results. It is well known that there is a rapid rise of cortisol in response to awakening that peaks after approximately 30 min. The cortisol awakening response is considered a reliable marker of the dynamics of the HPA axis and demonstrates moderate to high within-subject stability (Pruessner et al., 1997; Wuest et al., 2000; Edwards et al., 2001). The awakening response appears to be independent from diurnal cortisol secretion and cortisol responses to stress, though it is correlated with the response to standard adrenocorticotropin stimulation, suggesting that the cortisol awakening response is a marker for adrenocortical reactivity (Schmidt-Reinwald et al., 1999; Edwards et al., 2001). In clinical studies, the cortisol awakening response has been found to be increased in euthymic patients with a history of major depression (Bhagwagar et al., 2003), possibly reflecting risk for depression. Decreased cortisol awakening responses have been reported for subjects with chronic stress (Schulz et al., 1998), burnout (Pruessner et al., 1999), chronic pain (Geiss et al., 1997) or posttraumatic stress disorder (Rohleder et al., 2004), and other health problems (Kudielka and Kirschbaum, 2003). The morning cortisol response has never been studied in adults with early adverse experience. Altered cortisol awakening responses as a function of early adversity, such as ELE, might convey risk for one or another of the above disorders and might be a