Psychoneuroendocrinology (2005) **30**, 199–211

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Habituation of cortisol responses to repeated psychosocial stress—further characterization and impact of genetic factors

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Received 5 April 2004; received in revised form 4 July 2004; accepted 5 July 2004

KEYWORDS
Hypothalamus–pituitary–adrenal axis;
Trier Social Stress Test (TSST);
Heritability;
GR polymorphisms;
Pharmacological challenge

Summary Although a rapid response habituation to repeated stress exposure is a key characteristic of the hypothalamus–pituitary–adrenal (HPA) axis, several studies document a substantial inter-individual variability of such HPA response patterns. In order to further investigate the individual differences in the habituation of this important neuroendocrine system to psychosocial stress, 54 male twin pairs were exposed to moderate psychosocial stress on three occasions, each exposure separated by a 1-week interval. Additionally, an $ACTH_{1-24}$ stimulation test (1 μg) and a dexamethasone suppression test (0.5 mg) were performed. Although on average the expected decrease of mean cortisol and ACTH responses across stress exposures was observed, only 52% of the subjects showed this well-documented general decline and almost 16% of the participants even showed a response sensitization across sessions. Furthermore, a weak habituation was related to low cortisol responses to both the first stress exposure as well as the ACTH challenge. Moreover, genetic analyses did not reveal any evidence for a substantial heritability of the individual cortisol response habituation or an association between this habituation and two common polymorphisms in the glucocorticoid receptor gene.

1. Introduction

A common endocrine feature of the organism's response to psychological or physiological stress is the activation of the hypothalamus–pituitary–adrenal (HPA) axis including an increase of cortisol, the most important glucocorticoid in humans. Since chronic dysregulation of HPA axis activity seems to

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0306-4530/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2004.07.002

be associated with the onset and course of several psychosomatic and psychiatric disorders (Friedman et al., 1963; Buske-Kirschbaum et al., 1997; Yehuda, 1997; Bjorntorp and Rosmond, 1999; Chrousos, 2000; Holsboer, 2000; Belanoff et al., 2001; Chu et al., 2001), it is important to identify the determinants of the marked inter- and intra-individual variation in this system. A key characteristic (Rose, 1980) of HPA functioning that has been frequently observed in both animals (Mason et al., 1968; De Boer et al., 1990; Schrader and Ladewig, 1999; Marti et al., 2001) and human subjects (Levine, 1978; Gunnar et al., 1989; Kirschbaum et al., 1995; Gerra et al., 2001) is a rapid habituation of responses after repeated exposure to (initially) stressful stimulation. However, a number of findings, most of them from animal studies, document that such a habituation of adrenocortical responses does not necessarily occur (Coe et al., 1983; Al'Absi et al., 1997; Dhabhar et al., 1997) and even sensitization was observed (Vogel and Jensh, 1988; Fuchs et al., 1995). Several reports suggest that on one hand, characteristics of the stressor are important mediators determining the development of habituation, including intensity (Natelson et al., 1988; Pitman et al., 1990; Marti et al., 2001) and frequency (De Souza and Van Loon, 1982; De Boer et al., 1990; Ma and Lightman, 1998) of stress administration.

On the other hand, differences between the exposed individuals also have a significant impact. Documenting the relevance of genetic differences, Dhabhar et al. (1997) observed a habituation of corticosterone responses to daily immobilization stress in Sprague-Dawley and Lewis rats, whereas in Fisher 344 rats, a strain that shows enhanced HPA axis responses to acute stress, no indication of habituation could be detected. Early life experiences as a source for inter-individual variability as well seems to be relevant for later adaptation of HPA axis responses to repeated stress exposure. Bhatnagar and Meaney (1995) found a reduction of ACTH (but not corticosterone) responses to repeated cold stress in adult, neonatally handled rats while no such adaptation was observed in non-handled animals. Furthermore, the magnitude of the individual corticosterone response to the initial stress exposure in rats was found to be positively related to the degree of habituation of responses to subsequent exposures (Natelson et al., 1988).

Also some findings in humans document a substantial inter-individual variability of HPA axis response patterns across repeated stress exposure. In a study by Kirschbaum et al. (1995) 35% of the subjects did not show a significant cortisol response decrement across five exposures to moderate psychosocial stress, and Gerra et al. (2001) did not observe a habituation of cortisol and ACTH responses to the second exposure to psychosocial stress in 40% of the participants; however, in both studies a response habituation was observed when the entire group was analyzed. Moreover, employing a rather intense stressor Deinzer et al. (1997) found a response reduction from the very first to the second and third parachute jump in about 50% of the subjects.

An insufficient ability to adjust or habituate to repeated exposure to the same stressor is considered as one condition that leads to allostatic load (McEwen, 1998). Allostasis means 'maintaining stability through change' (Sterling and Eyer, 1988) and allostatic load is the cumulative long-term effect of the physiological systems' attempts to adapt to life's demands (McEwen and Stellar, 1993; McEwen, 1998). It was recently demonstrated that the allostatic load index, consisting of 10 biological parameters including estimates of HPA axis activity, is positively associated with the risk for 7-year mortality as well as declines in cognitive and physical functioning (Seeman et al., 2001; Karlamangla et al., 2002).

Although the genetic load of the adaptation of HPA axis responses to repeated challenge has not yet been investigated in humans, evidence from quantitative genetic studies as well as association studies document a significant impact of genetic factors on other aspects of HPA axis functioning. Twin studies consistently found a moderate genetic effect on basal HPA axis activity (Maxwell et al., 1969; Meikle et al., 1988; Linkowski et al., 1993; Wüst et al., 2000a; Bartels et al., 2003). Studies on stimulated HPA axis activity yielded inconsistent results, probably at least in part due to methodological differences. While some reports argue against a large contribution of genetic factors on variation in stimulated cortisol and ACTH levels (Inglis et al., 1999; Froehlich et al., 2000), findings from our laboratory point towards a considerable genetic effect on some aspects of HPA axis reactivity. Kirschbaum et al. (1992a) reported a pronounced influence of genetic factors on salivary cortisol responses after administration of 100 μg CRH. Furthermore, recent findings suggest a substantial heritability of free and total cortisol as well as ACTH responses to repeated exposure to psychosocial stress. (Federenko et al., unpublished data).

Moreover, accumulating evidence suggests that variants of the glucocorticoid receptor (GR) gene that affect a cell's sensitivity for glucocorticoids (GCs) contribute significantly to the large inter-individual variability of HPA axis activity in 'normal', non-clinical populations (DeRijk et al., 2002).