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Sex-specific adaptation of endocrine and inflammatory responses to repeated nauseogenic body rotation

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Summary It has been shown that stress changes stimulated pro-inflammatory cytokine production and the sensitivity of stimulated cytokine production to glucocorticoid suppression. While glucocorticoid secretion habituates in response repeated stimulation, it is not known whether stimulation and suppression of cytokine production are also subject to adaptation.

Eight healthy young subjects were exposed to repeated nauseogenic body rotation on four consecutive days. On each day subjects were rotated around the vertical axis up to five times for a period of 1 min or until subjects chose to stop due to nausea. Blood and saliva samples were obtained before and after rotation for assessment of cortisol, ACTH, plasma vasopressin (ADH), in vitro TNF-α and IL-6 production and glucocorticoid sensitivity of TNF-α and IL-6 production.

Rotation induced increases of ACTH, cortisol, and ADH in the first session. All endocrine responses habituated over time, except for the free cortisol response in men. Pro-inflammatory cytokine production showed a sex-specific response pattern with increases in men and decreases in women in the first session vs. increases in men and women in the last session. Response patterns of GC sensitivity also changed over time: in the first session, sensitivity increased only in men, but in the last session, GC sensitivity decreased in all subjects.

In conclusion, in response to repeated nausea induction, habituation occurs only in the endocrine system and predominantly in women. In the immune system, response patterns change in the favor of inflammatory conditions, with increases in stimulated IL-6 and TNF-α and decreases in the effectiveness of glucocorticoid suppression of

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these cytokines. These presumably unfavorable changes in the inflammatory system are more pronounced men.

1. Introduction

Psychosocial stress is a potent activator of central and peripheral stress systems, such as the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system. We and others have found that HPA axis responses to psychosocial stress show a rapid habituation after repeated exposure to acute laboratory stress tasks (Kirschbaum et al., 1995; Schommer et al., 2003) in human subjects, or repeated adverse stimuli in animal studies (Mason et al., 1968). In contrast to the HPA axis, results for the sympatho-adrenal medullary system (SAM) are less consistent, with some studies showing habituation (Konarska et al., 1989), while others could not (Schommer et al., 2003). Habituation of responses after repeated exposure to similar situations is an important mechanism for preventing detrimental health outcomes, which according to the concept of allostatic load are the result of inappropriately high or low levels of stress mediators (McEwen, 2000).

Inappropriately low levels of cortisol, for example, are believed to lead to a disinhibition of inflammatory processes, thereby mediating exacerbations of atopic, inflammatory, or autoimmune diseases (Del Rey and Besedovsky, 2000; Sapolsky et al., 2000). Recent reports have shown that the simple measurement of peripheral stress mediators may be insufficient, as large variation of target tissue sensitivity towards hormone effects may occur. Inter- and intraindividual variation has been reported for the sensitivity of diverse immune cells towards glucocorticoid effects (Rohleder et al., 2003).

Baseline differences in glucocorticoid sensitivity exist for example between patients suffering from stress-related psychiatric diseases and healthy controls. Traumatized civil war refugees with posttraumatic stress disorder (PTSD) have been shown to have lower circulating cortisol levels accompanied by an increased LPS stimulated production of inflammatory cytokines and an increased glucocorticoid sensitivity of cytokine production, which was interpreted as insufficient compensation of low cortisol (Rohleder et al., 2004). In a sample of clinically depressed women, Miller et al. reported the same phenomenon at baseline, i.e. an increased sensitivity of inflammatory cytokine producing cells, but a glucocorticoid resistance developing in response to psychosocial stress (Miller et al., in press). In an earlier study, the same group reported decreased glucocorticoid sensitivity of IL-6 production in a sample of people suffering from the chronic stress of care giving (Miller et al., 2002). It was further shown that glucocorticoid sensitivity varies with several parameters associated with risk factors for cardiovascular diseases. GC sensitivity was found decreased in industrial workers with vital exhaustion (Wirtz et al., 2003), and in middle-aged men with hypertension, pointing to the importance of the ability to effectively suppress inflammatory responses (Wirtz et al., 2004). While these studies have shown that sensitivity shows long-term alterations in between people suffering from PTSD, depression, chronic stress, hypertension, and vital exhaustion, it is furthermore of interest to describe short-term adaptive responses of inflammatory cytokine production.

We have shown in a first study that acute stress increases GC sensitivity of cytokine production in men, while it induces decreases in women and elderly men. The increases of sensitivity in men have been interpreted as protective against overshooting immune responses, while the decreases in women could be one factor mediating the higher prevalence of inflammatory diseases in women (Rohleder et al., 2002; Rohleder et al., 2001). No studies have so far directly investigated whether habituation occurs in these systems after repeated stress exposures. Dugue and Leppänen, however, showed that people who were used to swim in ice-cold water after sauna bathing showed higher increases in stimulated pro-inflammatory cytokine release than inexperienced winter swimmers (Dugue and Leppanen, 2000). This could be interpreted as indirect evidence for sensitization of pro-inflammatory cytokine release in response to repeated physiological loads.

We have previously reported that motion sickness induced by exposing human subjects to rotation around the vertical axis also activates the HPA axis to a similar extent as psychosocial stress (Klosterhalfen et al., 2000). Motion sickness is described as the final result of a 'central conflict' between different sensory inputs to the CNS during rotation (Probst and Schmidt, 1998). The severity of