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Impact of oral contraceptive use on glucocorticoid sensitivity of pro-inflammatory cytokine production after psychosocial stress

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Abstract

We previously reported that women using oral contraceptives (OC) show blunted free cortisol responses to psychosocial stress compared to medication-free women. Low cortisol responses to stress have been shown to be associated with increased susceptibilities to chronic inflammatory and autoimmune processes in animal models and certain human diseases.

To address the question if the blunted free cortisol response of OC users may be compensated at the level of the target tissue, we measured hypothalamus–pituitary–adrenal (HPA) axis activation and glucocorticoid (GC) sensitivity of pro-inflammatory cytokine production after psychosocial stress in 14 women using OC and 11 women in the luteal phase of the menstrual cycle.

All subjects were exposed to the psychosocial stress paradigm 'Trier Social Stress Test' (TSST). Free cortisol was measured repeatedly before and after stress. GC sensitivity was assessed by dexamethasone (DEX) inhibition of lipopolysaccharide (LPS) stimulated production of interleukin-6 (IL-6) in whole blood, immediately before, as well as 10 and 60 min after the stress test.

As expected, the stress test induced significant increases in free cortisol in luteal phase women, while OC users showed blunted responses ($F = 3.31; p < 0.05$). GC sensitivity showed different response patterns; In luteal phase women a slight but not significant decrease was observed throughout the experiment. In contrast, women using OC showed a significant increase in GC sensitivity after stress ($F = 3.559; p < 0.05$).

These results show, that an increase in GC sensitivity of pro-inflammatory cytokine production may at least in part compensate the low cortisol levels seen in OC users after stress.

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This could be one mechanism to protect women using OC medication from chronic inflammatory and autoimmune diseases.

Keywords: Oral contraceptives; Stress; Glucocorticoid sensitivity; Pro-inflammatory cytokines; Humans; Gonadal steroids

1. Introduction

Women using oral contraceptives (OC) show a blunted free cortisol response to psychosocial stress compared to men and regularly cycling women (Kirschbaum et al., 1999). This seems to be mediated by increased levels of corticosteroid-binding globulin (CBG) (Wiegratz et al., 1995; Crook, 1997), since total plasma levels of cortisol do not differ between these groups.

Activation of the HPA axis after psychological and physiological stress seems to be an important mechanism for the maintenance of health, since genetically determined low glucocorticoid (GC) responses to a variety of stressors are associated with increased susceptibilities to certain immune related diseases. For example, rat strains showing blunted corticosterone responses to experimentally induced autoimmune diseases show increased susceptibilities to and death from these diseases, while strains with normal or high corticosterone responses rapidly recover within few days (Sternberg et al., 1989; Mason, 1991; Cizza and Sternberg, 1994). Low cortisol responses to stress are also reported in some human autoimmune and inflammatory diseases, such as atopic dermatitis (Rupprecht et al., 1995; Buske-Kirschbaum et al., 1997; Rupprecht et al., 1997; Buske-Kirschbaum et al., 2001). In rheumatoid arthritis, some results indicate decreased HPA axis responses to the stress of surgery (Chikanza et al., 1992), while a recent review suggests that the majority of the findings hint to a normal basal and reactive HPA axis in rheumatoid arthritis (Harbuz and Jessop, 1999).

These results clearly underline the importance of the HPA axis as a negative feedback loop, in which inflammatory cytokines stimulate the hypothalamus to activate pituitary–adrenal function, which in turn results in GC mediated restraint of the immune response (Munck et al., 1984). The correct timing of the GC increase and effectiveness, e.g. as a ‘second wave’ of stress mediators with a time lag of about 10–20 min before being increased, and more than an hour of being effective at the target cell level, is thought to be required for protecting the individual from an overshooting of inflammatory cytokines with potentially detrimental effects on the host (Sapolsky et al., 2000; Besedovsky and del Rey, 2000).

In light of this regulatory loop and the blunted cortisol responses to stress in women using OC, the question arises whether these individuals are more susceptible to chronic inflammatory or autoimmune diseases. In fact, OC use has been reported to exert mild protective effects in organ-specific autoimmune diseases like rheumatoid arthritis (Van Vollenhoven and McGuire, 1994), while a negative impact is observed in antibody mediated autoimmune diseases, like systemic lupus erythematosus