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Glucocorticoid Sensitivity in Humans-Interindividual Differences and Acute Stress Effects

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The hypothalamus pituitary adrenal (HPA)- axis is one of the major output systems of the neuroendocrine stress response. Its major end products, glucocorticoids (GCs), have a plethora of effects throughout the organism, most of which are believed to be protective against disturbances of homeostasis. However, negative effects have also been described under specific conditions of hyper- or hypo(re)activity of the HPA axis. Both beneficial and adverse effects of GCs ultimately depend on the target tissue sensitivity to these steroids. Recent findings suggest that GC sensitivity (a) may vary between different target tissues in the same organism, (b) shows large individual differences and (c) can be acutely changed in times of acute stress.

In the present review, data are summarized which show differences in GC sensitivities in patients suffering from diverse somatic and psychiatric diseases, as well as chronically stressed individuals. Furthermore, studies are presented that show a rapid modulation of GC sensitivity in response to exercise or psychosocial stress in healthy adults. The response pattern of acute GC sensitivity modulation seems to be influenced by age and sex hormone status of the individual. While the GC signalling cascade may be subject to modulation at several levels, the pathway for acute modulation of GC sensitivity remains to be elucidated.

Keywords: Stress; Glucocorticoid sensitivity; Cortisol; Human; Cytokines; HPA axis

INTRODUCTION

The endocrine and the immune systems play major roles in the adaptation of any organism to outside forces that are threatening the stability or homeostasis of the internal milieu (Chrousos, 2000). An important neuroendocrine system involved in this adaptive response is the hypothalamus pituitary adrenal (HPA) axis with its major endocrine end product, the stress hormone cortisol or in rodents, corticosterone. After Selye introduced the term "Stress" in 1936 (Selye, 1936; 1956), literally thousands of studies have been published on the impact of diverse events in the life of an organism on the (re)activity of the HPA axis. Psychological stress, whether chronic or acute, has been identified as a major activator of this neuroendocrine system (Mason, 1968; Pacak and Palkovits, 2001).

Furthermore, a large array of studies has focused on the functions of glucocorticoids (GCs). As summarized by Munck and Sapolsky (Munck *et al.*, 1984; Sapolsky *et al.*, 2000), the effects of GCs in any acute stressful situation can be classified as protective for the organism (preserving homeostasis) against the negative sequelae of stress, at least if considered over the short term. However, in the long term, adverse effects of GCs and other stress mediators have been identified. According to the allostatic load model, stress hormones may exert deleterious effects in the organism, if activated for too long, too often, too excessively, or if there is insufficient secretion, or without compensation by other mediators. The resulting imbalances put strain on the organism, which is then referred to as "wear and tear" or allostatic load (McEwen, 2000).

Accordingly, changes in basal as well as stimulated levels of GCs are commonly reported to be associated with different disease processes or susceptibilities towards different diseases in animals and humans. Chrousos *et al.* report increased HPA axis activity in individuals suffering from chronic stress, depression, panic disorder, alcoholism, anorexia nervosa and many more, while decreased HPA axis activity is identified in individuals with adrenal insufficiency, fibromyalgia, and in the postpartum period, for example (Chrousos, 1998). An excellent example of

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the importance of intact HPA axis responses is the role of GCs in brain-immune system communication. If a laboratory animal is unable to mount a sufficient HPA axis response to an inflammatory stimulus, then it is at much greater risk to suffer from (or even die of) the resulting inflammation (Besedovsky and del Rey, 2000; Sternberg, 2001). While such a causal relationship between stress, GC responses and disease is well documented in animal models, only sparse correlational evidence exists for humans thus far. In line with the animal data, patients suffering from atopic diseases have been found to show lower cortisol responses to psychosocial stress compared with healthy controls (Buske-Kirschbaum *et al.*, 1998). Similar clear-cut data are not available for other chronic inflammatory or autoimmune diseases. Most but not all results imply a decreased activity of the HPA axis in patients with rheumatoid arthritis or fibromyalgia (Chikanza *et al.*, 1992; Crofford *et al.*, 1994; Michelson *et al.*, 1994; Dekkers *et al.*, 2001), while in multiple sclerosis, more reports indicate an exaggerated HPA axis response (Grasser *et al.*, 1996; Then Bergh *et al.*, 1999)

Relating to the potentially deleterious effects of GCs on the body, most stress theories implicitly assume that any given GC level equally affects different target tissues throughout the organism. However, there are several reasons to believe that this is an oversimplification. Accumulating evidence suggests that in addition to peripheral cortisol levels, GC sensitivity of the individual target tissues must also be considered when speculating about the potential health risks associated with a hyper- or hyporeactive HPA axis (DeRijk and Sternberg, 1997).

The first line of evidence stems from the clinical observation that a substantial proportion of patients suffering from chronic inflammatory diseases do not adequately respond to GC medication (Brönnegard *et al.*, 1996a,b). Such GC resistance has been observed in rheumatoid arthritis (Chikanza *et al.*, 1992; Schlaghecke *et al.*, 1992), systemic lupus erythematosus (Tanaka *et al.*, 1992), and is best described in bronchial asthma (Wilkinson *et al.*, 1989). The second line of evidence emerges from our increasing understanding of the underlying mechanisms of GC signal transduction. In brief, the effect of any hormone on its respective target cell depends on the extra- and intracellular hormone availability, the potency of the hormone, and the ability of the cell to receive and transduce the signal. According to Bamberger and coworkers, the latter is referred to as the responsiveness of the cell, while the sensitivity of the cell is determined by a large array of intracellular factors, which can modulate the signal transduction cascade at nearly every level. The extent to which an *a-priori* responsive system responds to GCs is called GC sensitivity (Bamberger *et al.*, 1996).

While the possibility of inter- and intraindividual differences in GC sensitivity becomes more and more accepted, different methods have been developed to assess GC sensitivity in different target tissues (Ebrecht *et al.*, 2000). The first and most common method to investigate GC sensitivity is to measure the sensitivity of the HPA axis to negative feedback exerted by its own end product. The peripheral administration of dexamethasone (DEX) in the dexamethasone suppression test (DST) is a widely used method to investigate the integrity of HPA axis feedback regulation (Maguire *et al.*, 1987). It has so far been employed in patients suffering from different somatic or psychiatric diseases, such as depression (Lowy *et al.*, 1984), posttraumatic stress disorder (PTSD) (Yehuda *et al.*, 1993), or obesity (Jessop *et al.*, 2001), as well as in healthy subjects (Huizenga *et al.*, 1998b). The results of the DST can be interpreted as an index of the GC sensitivity of the HPA axis (Ebrecht *et al.*, 2000).

Another target tissue for GCs is the vascular cell wall, in which GCs serve to increase the vascular tone. Adrenalectomized animals or patients with GC deficiency have been reported to show decreased blood pressure responses that are reversed by treatment with DEX or hydrocortisone (Walker and Williams, 1992). Based on these effects, an assay was developed to assess the vasoconstrictive response of blood vessels in the skin (McKenzie and Stoughton, 1962). In this test, different GC preparations are applied to the skin and covered overnight with foil. Depending on the potency of the GC preparation, the blood vessels of the skin constrict, which leads to blanching of the skin. The degree of blanching is correlated with the GC sensitivity of the vascular response. Studies using this assay revealed that in patients with hypertension, the dermal vasoconstrictor sensitivity to GCs is increased (Walker *et al.*, 1996). It was further shown that even the children of parents suffering from hypertension had an increased dermal GC sensitivity (Walker, 1996). While there seems to be a promising association of skin sensitivity to GC with indices of essential hypertension, GC sensitivity of the skin is not correlated with two other aspects of GC sensitivity, i.e. GC sensitivity of pro-inflammatory cytokine production, and HPA axis feedback sensitivity as measured by the DST (Ebrecht *et al.*, 2000).

The first experiments on the sensitivity of immune cells towards the suppressive capacity of GCs were done in 1977, when Smith and Munck (Smith *et al.*, 1977) measured glucose uptake by concanavalin A (ConA) -stimulated lymphocytes and inhibited this index of metabolism by addition of varying DEX concentrations. Later, DeRijk *et al.* and other groups developed an assay, in which lipopolysaccharide (LPS) -stimulated cytokine production in whole blood is inhibited by different concentrations of DEX (DeRijk *et al.*, 1996).

Common to all methods of measuring GC sensitivity is that a target tissue of interest is activated (if not already active, for example mitogens are used to stimulate immune cells), and an appropriate output measure is chosen which is then assessed alone and with different concentrations of synthetic GC preparations. This leads in most cases to a dose-dependent inhibition

of the output measure. The position, the slope, and the plateau levels of the dose-response curve are then interpreted as an index of GC sensitivity of the target tissue investigated.

Most measures of GC sensitivity use blood or immune cells extracted from the blood, or the skin, as these tissues are readily accessible. GCs have many actions beyond those on the cells and tissues of the immune system or the vasculature of the skin, for example on metabolism, cognition and behavior (Sapolsky *et al.*, 2000). However, methods to explicitly measure GC sensitivity of the tissues involved in these responses have not been developed.

MODULATION OF GC SENSITIVITY

For a better understanding of potential parameters that influence GC sensitivity, the underlying mechanism of immune cell activation by mitogens and the inhibition of activated immune cells by GCs will be described here as an example. The mechanisms in immune cells do not necessarily reflect those in other GC target tissues.

Activation of Cytokine Production

The activation of the main effector cells of the innate immune response, i.e. monocytes and macrophages, by LPS will be elaborated here, to facilitate insight into possible pathways by which GCs and other immunomodulators can suppress this process. The response of the cells of the innate immune system to microbial infection is an important mechanism of host defense. It is now widely accepted that molecular mechanisms of microbial recognition are "hard-wired" or programmed into the cells of the innate immune system and that these mechanisms have evolved through selective pressure exerted by pathogens (Medzhitov and Janeway, 1997). A variety of pattern recognition receptors has been proposed to recognize microbial structures, which include bacterial lipopolysaccharides, lipoproteins, lipotechoic acids, or viral double-stranded DNA. One of these is LPS, an essential component of gram-negative bacteria (Kitchens, 2000).

The mechanism of monocyte activation by LPS is shown in Fig. 1. LPS complexes in the circulating blood with soluble receptors, i.e. lipopolysaccharide binding protein (LBP) or the soluble form of the monocyte surface

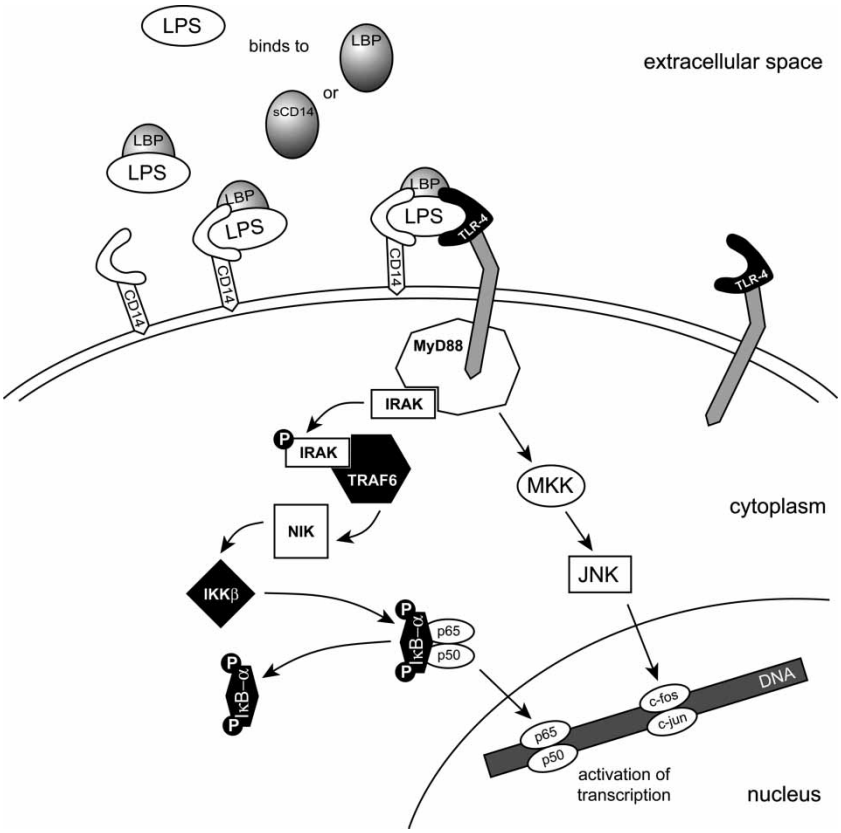

FIGURE 1 Mechanism of monocyte activation by lipopolysaccharide (LPS). (LBP: LPS binding protein; CD14: cluster of differentiation antigen 14; sCD14: soluble CD14; TLR-4: toll-like receptor-4; MyD88: myeloid differentiation factor-88; IRAK: IL-1 receptor associated kinase; TRAF6: TNF receptor associated factor-6; p50 and p65: two proteins of the nuclear factor (NF) -κB family; IκB-α: inhibitory κB-α; NIK: NF κB-inducing kinase; IKK: IκB-kinases; MKK: mitogen activated protein (MAP) kinase kinase; JNK: jun N-terminal kinase; c-fos and c-jun: two proteins of the activator protein (AP)-1 family) (modified from Grossmann *et al.* (1999) and Lewis and Manning (1999)).

protein CD (cluster of differentiation antigen) 14 (sCD14; (Swantek *et al.*, 2000). After binding to one of these soluble receptors, the complex binds to the surface molecule CD14 of monocytes and macrophages, which has long been proposed as the primary LPS receptor (Berczi, 1998; Berczi *et al.*, 2000). However, as CD14 does not possess a cytoplasmic domain, it was not resolved how LPS could activate the well-known cascade of effects (Beutler, 2000).

Recently, another receptor has been discovered, which transduces the LPS-signal through the outer membrane. The toll-like-receptor 4 (TLR-4) is the mammalian homologue of the *Drosophila* toll protein (Medzhitov *et al.*, 1997). The intracellular domain of TLR-4 is extremely similar to the cytoplasmic domain of the interleukin-1 receptor (IL-1R) and related molecules (Muzio and Mantovani, 2000). Therefore, the activation of monocytes and macrophages by LPS involves the same intracellular cascade as activation by interleukin (IL) -1. Upon interaction with LPS bound to CD14, the intracellular domain of TLR-4 binds to the adaptor protein myeloid differentiation factor-88 (MyD88), which consecutively binds to and activates the IL-1R associated kinase (IRAK). IRAK then becomes phosphorylated and binds to the tumor necrosis factor-α receptor (TNF-R) associated factor-6 (TRAF6), which then bridges to the nuclear factor (NF) κB-inducing kinase (NIK); (Bowie and O'Neill, 2000). NIK is one of several activators of a complex of proteins called "signalsome". The signalsome is a complex of different proteins from the family of inhibitory κB (IκB) -kinases (IKK), which, when activated, promote the phosphorylation and subsequent degradation of inhibitory κB-α(IκB-α) (Fischer *et al.*, 1999).

Degradation of IκB-α is the central step in activation of the transcription factor nuclear factor (NF) -κB. Dissociation of the most common NF-κB proteins p65 and p50 from IκB-α unmasks a nuclear localization signal (NLS). NF-κB then translocates to the nucleus, binds to κB-responsive DNA elements, and induces the transcription of a large array of monocyte and macrophage products (Hatada *et al.*, 2000). Among the gene products regulated by NF-κB are growth factors, such as granulocyte macrophage-colony stimulating factor (GM-CSF), cell adhesion molecules, such as inter-cellular adhesion molecule (ICAM) -1 and vascular cell adhesion molecule (VCAM), pro-inflammatory cytokines, especially IL-1, IL-2, IL-6, IL-8, and tumor necrosis factor (TNF) -α, and further transcriptional regulators, such as the protein IκB-α (McKay and Cidlowski, 1999). Induction of the latter functions to bind free NF-κB molecules in the nucleus and cytoplasm and thereby deactivate transcription through negative feedback (Chiao *et al.*, 1994).

Parallel to the pathway described above, MyD88 has been reported to activate the transcription factor activator protein (AP)-1 through activation of the mitogen-activated protein kinase (MAP kinase) and jun N-terminal kinase (JNK) pathway. Activation of AP-1 has similar effects as NF-κB, as both are important in the transcription of inflammatory genes (McKay and Cidlowski, 1999).

GC Inhibition of Cytokine Production

Inhibition of this cascade by GCs is the main mechanism of GC-mediated immune suppression. It should be noted, however, that not all GC effects on the immune system are of a suppressive nature. Cytokine receptors for example have been shown to be upregulated by GCs (Wiegers and Reul, 1998), which is also the case for cytokines with anti-inflammatory functions, e.g. IL-10 (Franchimont *et al.*, 1999b). For a better understanding of these mechanisms, in this section the general pathways of GC signal transduction will be described. Most of the known GC effects are mediated by the GC or type-II receptor (GR), and the mineralocorticoid or type-I receptor (MR). For GC effects on immune function, the GR appears to be the receptor of primary importance (Bamberger *et al.*, 1996).

GC Receptor Activation

The GR is retained in the cytoplasm as part of a multiprotein complex that consists of GR, various molecules of the heat shock protein (HSP) family, as well as other, less well characterized proteins (Pratt, 1993; Smith and Toft, 1993). In the absence of hormone, this complex undergoes a continual cycle of dissociation and reassociation (Hutchison *et al.*, 1994). The main function of the GR-HSP-complex is to keep the GR in an inactive but still ligand-activatable state (Bresnick *et al.*, 1989; Pratt, 1993). Like all lipophilic substances, GCs can easily cross the cell membrane, where they bind to the GR. The binding of hormone leads to conformational changes of the GR, which in turn induce dissociation of the GC–GR complex from the HSP complex, the hyper-phosphorylation of the GR, and the unmasking of a NLS, which causes nuclear translocation of the GC–GR complex (Picard and Yamamoto, 1987; Smith and Toft, 1993).

Mechanism of GC Receptor Action

In the classical mechanism the GC–GR complex binds to specific DNA sequences called GC response elements (GRE) in the promoter region of GC responsive genes, the transcription of which is then enhanced. Alternatively, negative GREs (nGREs) have been identified, in which binding of the activated GR induces inhibition rather than activation of transcription (Bamberger *et al.*, 1996). Interestingly, pro-inflammatory cytokine genes, which are important targets of GC inhibition, do not contain nGRE sequences. GC induced immune suppression is mediated via alternative mechanisms. The GC–GR complex is able to directly interact with other transcription factors, for example AP-1 or NF-κB proteins (p50, p65), both of which are important in activating the expression of pro-inflammatory

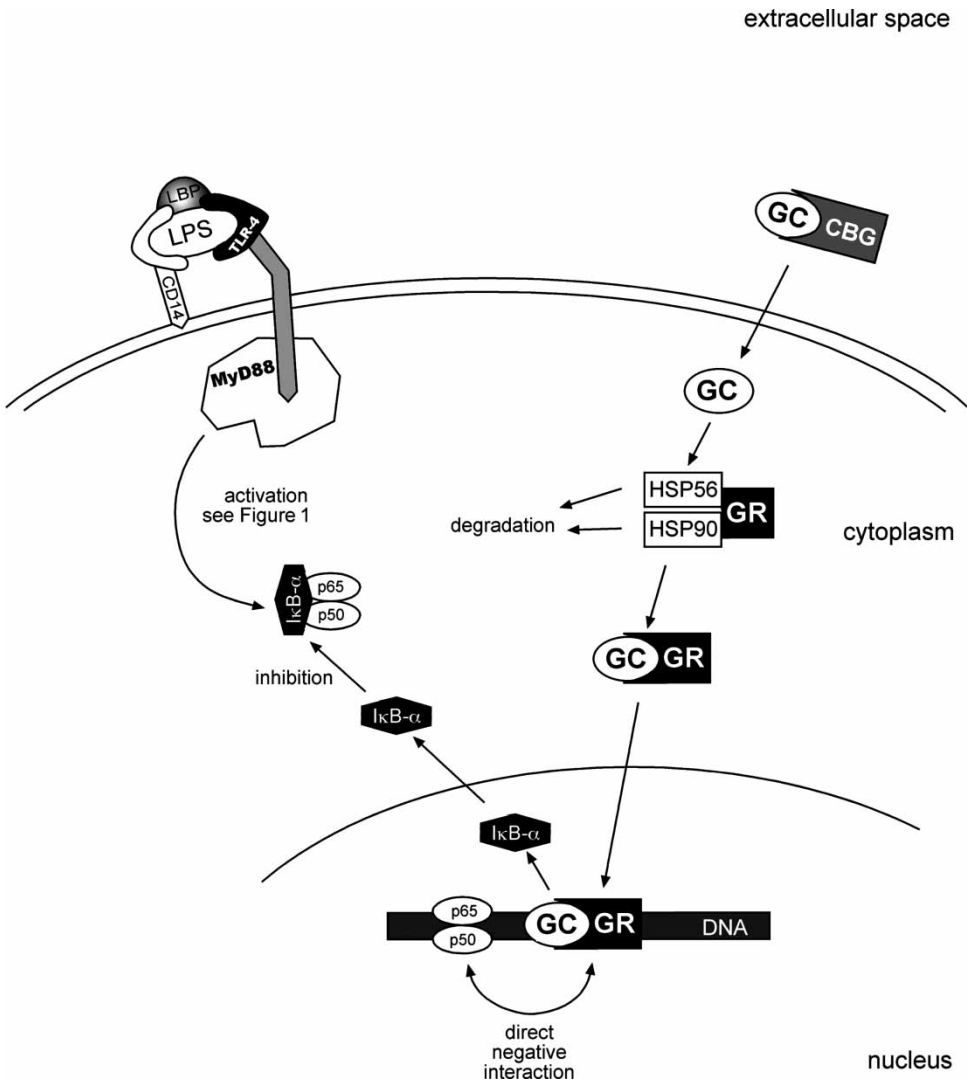

FIGURE 2 Mechanism of glucocorticoid inhibition of monocyte activation. (CBG: corticosteroid binding globulin; GC: glucocorticoid; GR: glucocorticoid receptor; HSP: heat shock proteins; see Fig. 1) (modified from McKay and Cidlowski (1999)).

and type-1 cytokines (see above; Heck *et al.*, 1994). This interaction leads to mutual inhibition of activity and thereby to inhibition of cytokine production (McKay and Cidlowski, 1998). Furthermore, GCs induce the expression of the inhibitory protein IκB-α, which is capable of deactivating NF-κB (Marx, 1995). This deactivation involves a redistribution of active p65 from the nucleus to the cytoplasm by masking of the NLS, and effectively down-regulates NF-κB associated gene products (Auphan *et al.*, 1995; Scheinman *et al.*, 1995). In summary, negative immune modulation by GCs involves inhibition of the transcription factors NF-κB and AP-1 by the activated GC–GR complex by two different mechanisms. The pathway of NF-κB inhibition is shown in Fig. 2.

Potential Pathways of GC Sensitivity Modulation

Given the complex pathways of monocyte activation by LPS and subsequent inhibition by GCs, several mechanisms can be proposed that are capable of modulating the GC sensitivity of pro-inflammatory cytokine production.

Extracellular Hormone Availability

Additional to the secretory rate induced by changes in circadian rhythm or stress and to application of synthetic GCs, extracellular hormone availability is determined by the presence of plasma binding proteins, such as corticosteroid binding globulin (CBG). It is well known that CBG levels are increased in women under oral contraceptive medication (Wiegratz *et al.*, 1995). Furthermore, short-term treatment with the cytokine IL-6 was shown to induce a rapid decrease of CBG levels in healthy volunteers (Tsigos *et al.*, 1998). This would predict an increased availability of GC during infection and thereby a higher efficacy of immune suppression.

Intracellular Hormone Availability

Another important factor is the intracellular hormone availability. Due to its lipophilic properties, GCs can easily pass the membrane of any target cell. However, inside the target cell specific enzymes, the 11-β-hydroxysteroid dehydrogenases (11β-HSD) are present, which catalyze the interconversion of active GCs (cortisol/corticosterone) to inactive forms (cortisone, 11-dehydrocorticosterone) and vice versa, and thereby determine GC access to the GR. Two isoforms have been detected, with 11β-HSD-1 producing the active hormone, and 11β-HSD2 producing the inactivated hormone (Seckl, 2000). It was shown in mice that knockout of 11β-HSD1 attenuates GC responsiveness (Kotelevtsev *et al.*, 1997). It is, therefore, hypothesized that also in humans, decreased availability of 11β-HSD1, or increased availability of 11β-HSD2 may decrease the GC sensitivity of target tissues (Bamberger *et al.*, 1996).

GC Receptor Expression Level

The number of receptors available in the respective cell determines the hormone-binding capacity of the cell. Furthermore, the sensitivity of a cell to GCs is closely correlated with the GR number or expression level (Vanderbilt *et al.*, 1987). Expression of GR not only varies between different tissues, but also can be further regulated by a variety of factors. GCs for example down-regulate receptor expression or reduce the half-life of the receptor-protein, and this may function as a short-loop negative feedback mechanism (Schmidt and Meyer, 1994).

Cytokines have been found to influence the expression of GR in a large number of studies using different human and rodent cell lines (including fibroblast cells lines [L929], promonocytic [U937] and B cell lines, [CESS] as well as human bronchial epithelial cells). The pro-inflammatory cytokines TNF-α, IL-1β, IL-1α, and IL-6 seem to upregulate the GR transcription (Rakasz *et al.*, 1993). Similar effects are found for the type-1 cytokines IL-2 and interferon (IFN) -γ (Salkowski and Vogel, 1992a; Sartori *et al.*, 1998), and for the anti-inflammatory cytokine IL-10 (Franchimont *et al.*, 1999b). This latter study was the only one to find a decreased GR number induced by the pro-inflammatory cytokine TNF-α. The bacterial endotoxin LPS itself was also shown to upregulate GR expression (Salkowski and Vogel, 1992b). Taken together, these results would predict that pro-inflammatory and type-1 cytokines increase the expression of the GR and thereby increase the GC sensitivity of the respective cell.

However, cytokines also influence the expression of GR-β, which is generated by alternative splicing of the human GR mRNA. This protein does not bind GCs and is transcriptionally inactive, but nevertheless is able to inhibit the DNA-binding activity of the ligand-activated GR-α. Increased expression of GR-β relative to GR-α can dose-dependently decrease GC sensitivity by up to 90% (Bamberger *et al.*, 1995). Combined treatment of human peripheral blood mononuclear cells (PBMC) with the cytokines IL-2 and IL-4 increased the expression of GR-β by more than 100% (Leung *et al.*, 1997). Webster *et al.* recently showed that the pro-inflammatory cytokines TNF-α and IL-1β increased expression of GR-α by 150%, while increasing GR-β expression by 350%, thus inducing a relative over-expression of GR-β (Webster *et al.*, 2001). In summary, these additional results would predict that pro-inflammatory cytokines would down-regulate GC sensitivity by induction of relative over-expression of the dominant negative isoform GR-β.

Hormone Binding Affinity

Another important aspect of successful GC signal transduction is the hormone binding affinity of the GR. Hormone binding affinity can be modulated by a large number of factors. Mutations of the GR gene are relatively rare and most often associated with GC resistance. GR polymorphisms on the other hand are reported to lead to less marked changes in GC sensitivity (DeRijk *et al.*, 2002). The Asn363Ser polymorphism for example has been found in 13 out of 216 volunteers and is associated with an increased feedback sensitivity of the HPA axis, a higher GC sensitivity of mitogen-stimulated lymphocyte proliferation, and a greater DEX-induced insulin response (Huizenga *et al.*, 1998a).

Hormone-binding affinity is furthermore determined by correct assembly of the GR-HSP complex, which serves to keep the GR in a ligand-friendly high affinity conformation (Pratt, 1993). One of the factors influencing the appropriate folding of the GR-HSP complex is the energy availability inside the cell. Thus adenosine triphosphate (ATP) depletion negatively influences folding of the GR-HSP complex (Orti *et al.*, 1992; Hu *et al.*, 1994). Furthermore, decreased expression of the HSP90 protein keeps the GR in a low affinity state (Picard *et al.*, 1990), and moreover, mutations of HSP90 negatively affect GR-HSP complex formation (Cadepond *et al.*, 1994; Nathan and Lindquist, 1995).

Immune system related factors also influence the ligand binding affinity of the GR. The immunosuppressive drug FK506 stabilizes the GR-HSP complex and thereby increases hormone-binding affinity and GC sensitivity (Ning and Sanchez, 1995). Cytokines have quite complex effects on hormone binding affinity. Using a large array of different cell lines, culture conditions, and assay techniques, it was shown that binding affinity was decreased by IL-2, IL-13 (Spahn *et al.*, 1996b), and by combinations of various cytokines, such as TNF-α and IL-6 or IL-1β (Rakasz *et al.*, 1993); IL-1β and IL-6 (Verheggen *et al.*, 1996); or IL-2 and IL-4 (Kam *et al.*, 1993). Conversely, increased affinities were reported after exclusive treatment with IL-1β, IL-6, or TNF-α (Rakasz *et al.*, 1993), with IL-1α (Pariante *et al.*, 1999), or with IFN-γ (Salkowski and Vogel, 1992a). In light of these complex data, Miller concluded in his review that

increases in GC sensitivity were more likely reported in studies using whole cell binding techniques, while studies using cytosolic radioligand binding assays predominantly reported decreases in GC sensitivity (Miller *et al.*, 1999). It is difficult to draw any clear-cut conclusions about cytokine effects on GC sensitivity.

GC Receptor Phosphorylation and Nuclear Translocation

Hyperphosphorylation of GR is an important event after GR activation, which is necessary to induce the nuclear translocation process (Orti *et al.*, 1992). Defects in phosphorylation would probably decrease GR translocation and thus GC sensitivity; however, this remains to be investigated. Additional factors have been identified that modulate nuclear translocation of the GR. The immune suppressive drugs FK506 and cyclosporin A both stimulate nuclear translocation of the receptor (Hutchison *et al.*, 1993; Ning and Sanchez, 1995; Renoir *et al.*, 1995). The pro-inflammatory cytokine IL-1, on the other hand, decreases GR translocation to the nucleus (Pariante *et al.*, 1999).

DNA/GRE Binding

The classical pathway of GR mediated gene transcription, i.e. binding to GREs or nGREs can be modulated by a number of factors. However, most of the factors summarized by Bamberger *et al.* (1996) have not yet been detected in human cell lines. Some studies revealed that activation of the protein kinase A pathway increased GR mediated transcription (Rangarajan *et al.*, 1992; Espinas *et al.*, 1995). The pro-inflammatory cytokine TNF-α was found to increase transcriptional activity in cells transfected with a GC reporter plasmid (Costas *et al.*, 1996). Pariante on the other hand reported a decreased GR-mediated gene transcription in L929 mouse fibroblasts after IL-1 treatment (Pariante *et al.*, 1999). No studies are currently available that report on factors influencing GR mediated transcription of the inhibitory protein IκB-α, which would be of considerable interest for GC sensitivity of pro-inflammatory cytokine production.

Interaction with Transcription Factors

Reflecting mutual transcriptional antagonism, the transcription factor NF κB represses the DNA-binding activity of GR to the same extent as activated GR can repress the DNA binding activity of NF κB. Further studies revealed that the p65 subunit of NF κB, and not p50, is responsible for repressing GR activity (Ray and Prefontaine, 1994; McKay and Cidlowski, 1998). More recent studies provide evidence that this functional antagonism is not simply the result of physical interaction, but involves transcriptional cofactors. These molecules termed coactivators and corepressors of transcription (McKenna *et al.*, 1999) interact with nuclear receptors and enhance or lower the transcription rate of their target genes. One theory proposes that the transcriptional activity of GR and NF κB depends on a common cofactor, which is present in limited supply in the nucleus. Activation of one of the transcription factors would then bind all available cofactor, reducing the transcriptional activity of the other transcription factor (McKay and Cidlowski, 1999). One candidate for this cofactor role at present is the cyclic adenosine monophosphate (cAMP) -response element binding protein (CBP/p300; (Yao *et al.*, 1996). Interestingly, CBP has also been shown to be necessary for successful transcriptional activity of the second pro-inflammatory transcription factor, AP-1 (Kamei *et al.*, 1996). Regardless of the mechanism, the mutual transcriptional antagonism of NF κB, potentially AP-1, and the GR also implies that activation of an inflammatory response should decrease the GC sensitivity of the respective tissue.

Summary of GC Sensitivity Modulation

In summary, GC sensitivity can be modulated at nearly every level of the GC signal transduction pathway. The multitude of factors that are involved at the respective levels, and conflicting results imply that an appropriate assessment of GC sensitivity should optimally determine all of the potential mechanisms. Since this is not possible from an economical point of view, while it can be suspected that only a few of the cofactors are known at present, the most promising way to assess GC sensitivity is to simply measure the relationship between a specific input, e.g. different concentrations of GCs, and the respective output, for example cytokine production or lymphocyte proliferation. One weakness of the methods described here is that they mainly investigate suppressive effects of GR, while most modulatory influences involve transactivating functions of GR.

EMPIRICAL STUDIES ON GC SENSITIVITY

Since the early investigation of Smith *et al.* (1977), a number of studies have investigated the GC sensitivity of immune cells in diverse conditions in animals and humans. Basal GC sensitivity has been investigated in a large number of studies: over the course of human development, as a function of the circadian rhythm, and in a number of conditions ranging from chronic stress through psychiatric diseases, such as depression and post-traumatic stress disorder, to somatic diseases like rheumatoid arthritis and HIV infection. However, acute modulation of GC sensitivity has only been investigated in a small number of studies.

Basal GC Sensitivity

Age Differences in GC Sensitivity

Kavelaars *et al.* investigated the GC sensitivity of phytohaemagglutinin (PHA)- and anti-CD3 stimulated

lymphocyte proliferation in whole blood and in isolated T lymphocytes of neonates, infants at the age of 1 week, 2–4 months, 5–8 months, 9–15 months, and in adults. The immature immune system of neonates and 1-week-old infants was shown to have a significantly increased sensitivity to GC suppression as compared to that of older children and adults. GC sensitivity decreased with advancing age to reach adult levels at the age of 9–15 months (Kavelaars *et al.*, 1995). Comparing the GC sensitivity of LPS-stimulated IL-1β, IL-1ra, and soluble IL-1 receptor (sIL-1R) production by PBMC between adults and elderly subjects, the study of Daun *et al.*, failed to show any significant changes in later life (Daun *et al.*, 2000).

Circadian Variation of GC Sensitivity

So far only two studies have investigated whether the well-established circadian variations of GC secretion are accompanied by changes in GC sensitivity. DeRijk *et al.* studied the GC sensitivity of LPS-induced secretion of IL-6, IL-1 and TNF-α in six healthy subjects in the morning (08:00–08:30 h) and in the evening (20:00–20:30 h). While no significant differences were found for IL-1 and IL-6, TNF-α production was significantly higher in the evening. Changes in GC sensitivity were not reported (DeRijk *et al.*, 1997). In a recent study including more subjects ($n = 37$), Gratsias reported that GC sensitivity of LPS induced TNF-α production in whole blood was higher in the morning and lower in the evening (Gratsias *et al.*, 2000).

GC Sensitivity in Psychiatric and Somatic Diseases

A number of studies furthermore investigated basal GC sensitivity in patients suffering from somatic or psychiatric diseases. Sauer *et al.* studied GC sensitivity of PHA-induced IL-2 production by PBMCs of patients with HPA axis pathologies, with either decreased or increased basal cortisol secretion, e.g. adrenal insufficiency and Cushing's disease. Hypocortisolaemic patients showed a tendency towards a decreased GC sensitivity, while hypercortisolaemic patients did not differ significantly from healthy controls (Sauer *et al.*, 1995).

Visser and coworkers investigated patients suffering from chronic fatigue syndrome in a series of studies. They reported that GC sensitivity of PHA-stimulated proliferation and IL-4 production of purified CD4 T lymphocytes was increased in chronic fatigue syndrome patients compared to controls, while no changes were reported for IFN-γ (Visser *et al.*, 1998). In a later study, employing a whole blood assay with LPS-stimulation, they further showed an increased GC sensitivity of IL-10, but not IL-12 production (Visser *et al.*, 2001a). These results were replicated in a further study, in which they additionally reported that the differences in GC sensitivity were not attributable to variation of GR expression or binding affinity (Visser *et al.*, 2001b). Accordingly, Gaab *et al.* recently found increased GC sensitivity of LPS-stimulated IL-6 and TNF-α secretion in another group of CFS patients (Gaab *et al.*, in press). In contrast to these findings Kavelaars *et al.*, report a decreased GC sensitivity of PHA-induced lymphocyte proliferation measured in adolescent girls suffering from chronic fatigue syndrome (Kavelaars *et al.*, 2000). This discrepancy may be explained by the different culture conditions used for the proliferation assays (whole blood vs. PBMC) or simply by the differences in the population studied (adolescent girls vs. mixed sex patients with mean age of 38 years.). A study on the related syndrome of fibromyalgia failed to reveal any differences in GC sensitivity of PHA-induced lymphocyte proliferation as compared to controls (Lentjes *et al.*, 1997).

In an early investigation of GC sensitivity in depressed patients, Lowy reported that *in vivo* administration of DEX failed to suppress subsequent PHA-stimulated lymphocyte proliferation in 8 of 12 patients suffering from major depression, but only in one of 12 control subjects, concluding a decreased GC sensitivity in depression (Lowy *et al.*, 1984). In a very recent study on patients with treatment-resistant depression, Bauer *et al.* reported a decreased GC sensitivity of PHA-induced PBMC proliferation and IL-2 production as well as LPS-induced TNF-α production (Bauer *et al.*, 2003).

Basal GC sensitivity has also been investigated in chronic inflammatory diseases. Heijnen *et al.* reported that rheumatoid arthritis patients show an increased GC sensitivity of PHA-induced lymphocyte proliferation in whole blood (Heijnen and Kavelaars, 2000). Steroid-resistant asthma patients were shown to have a decreased GC sensitivity of PHA-induced lymphocyte proliferation compared to steroid-sensitive asthma patients (Spahn *et al.*, 1996a). In Crohn's disease, Franchimont reports a decreased GC sensitivity of TNF-α, IL-6, and IL-1β production compared to healthy controls (Franchimont *et al.*, 1999a). Taken together, the results on inflammatory diseases used too diverse methods to come to a clear conclusion, and disease-specific differences in GC sensitivity cannot be excluded.

Chronic Stress

The effects of psychosocial stress on GC sensitivity have so far been investigated in three studies, all using chronic rather than acute stress paradigms. Sauer *et al.* investigated GC sensitivity of PHA-stimulated PBMC proliferation in 11 healthy students one hour before an academic examination and on a control day, during a holiday period. GC sensitivity was found significantly decreased on days with academic examination stress (Sauer *et al.*, 1995). Miller *et al.*, recently reported that parents of children suffering from cancer, who were significantly more distressed than control parents of medically healthy children, and suffered from greater overall negative and lower overall positive affect, had a decreased GC sensitivity of LPS-stimulated IL-6 production in whole

blood. Sensitivity of IL-1β and TNF-α, however, did not show any group differences (Miller *et al.*, 2002). In another study on the effects of chronic stress, Bauer *et al.*, correspondingly reported a decreased GC sensitivity of PHA-stimulated IL-2 production by PBMC cultures of elderly caregiver spouses of dementia patients (Bauer *et al.*, 2000). Taken together, chronic stress in humans seems to induce a decrease in GC sensitivity of different immune cell targets.

Acute Modulation of GC Sensitivity

Exercise

Most previous work on acute changes of GC sensitivity relied on diverse exercise paradigms to induce endocrine stress responses. DeRijk *et al.* used exposure to graded levels of exercise on a treadmill. They showed that after exercise, more DEX was needed for inhibition of LPS-induced IL-6 production in whole blood, i.e. the GC sensitivity was decreased by exercise (DeRijk *et al.*, 1996). They further reported that LPS-induced production of IL-1 and TNF-α, but not of IL-6, was reduced after exposure to exercise of high intensity. They concluded that GC sensitivity of production of the former cytokines increased after exercise, while that of the latter cytokine was resistant. Unfortunately, a direct assessment of GC sensitivity by co-incubation with DEX or hydrocortisone was not performed, so that these results have to be interpreted with caution (DeRijk *et al.*, 1997). Smits *et al.* studied the variability of GC sensitivity of LPS-stimulated production of IL-6, IL-10, and TNF-α in response to strenuous exercise of endurance-trained men on a rowing ergometer for 15–20 min. They found a decrease in GC sensitivity of IL-6 and TNF-α, but not of IL-10 after exercise (Smits *et al.*, 1998). Duclos *et al.*, investigated the effect of a 2h run in trained men, compared to resting in untrained men, on GC sensitivity of LPS-stimulated IL-6 production by isolated cultured monocytes. In contrast to the results of DeRijk and Smits, they found an increase in GC sensitivity after exercise. These discrepancies may be the result of the different culture conditions (i.e. isolated monocytes instead of whole blood), the apparently longer period of exercise or differences in the subjects studied, for example their age or gender (Duclos *et al.*, 1999).

Psychosocial Stress

The effects of acute psychosocial stress have been investigated predominantly in animals. Sheridan and coworkers employed a social disruption stress (SDR) model in male C57BL/6 mice and studied subsequent changes in the GC sensitivity of splenocyte proliferation. In the SDR stress model, male mice are housed in groups of five for two weeks, until a stable social hierarchy has developed. The dominant mouse is then transferred to another cage, in which it behaves as an aggressive intruder. Thereby, the social hierarchy is disrupted and excessive fighting starts to re-establish a social hierarchy, which is stressful for the intruder as well as for the resident mice (Sheridan *et al.*, 2000). In a series of studies, it was shown that SDR stress, and conventional restraint stress, induce significant activation of the HPA axis. SDR, but not restraint stress, furthermore leads to GC resistance in the proliferative response of splenocytes to LPS (Stark *et al.*, 2001). This GC resistance develops only after repeated exposure to SDR and lasts for up to ten days after the last SDR exposure (Avitsur *et al.*, 2002). It is accompanied by an increased mortality from experimental influenza viral infection (Sheridan *et al.*, 2000), and septic shock induced by an intraperitoneal LPS injection (Quan *et al.*, 2001). The development of GC resistance was most pronounced in animals that showed subordinate behavioral patterns and a higher number of injuries due to fighting (Avitsur *et al.*, 2001), and could not be replicated for peritoneal macrophages (Avitsur *et al.*, 2002).

Bauer *et al.* investigated GC sensitivity of PHA-stimulated splenocyte and blood lymphocyte proliferation in laboratory rats after acute and repeated exposure to restraint stress. In contrast to the data cited above, their results were less clear; GC sensitivity slightly increased after repeated exposure to restraint stress in splenocytes, but not in peripheral blood lymphocytes. Acute stress did not induce any significant changes in GC sensitivity (Bauer *et al.*, 2001).

Acute psychosocial stress in humans has only been investigated in three studies so far. In all of these studies, healthy human subjects were exposed to a psychosocial stress paradigm, the "Trier Social Stress Test" (TSST), to elicit a profound activation of neuroendocrine stress systems. The TSST is a short laboratory stress paradigm in which subjects are asked to deliver a free speech as in a job interview for 5 min and afterwards have to complete a difficult mental arithmetic task (serial subtraction of the number 17 from 2043) for another 5 min. This is done in a separate room in front of a committee of psychologists trained in behavioral assessments. The whole performance is furthermore videotaped for later analysis. After explanation of the procedure, the subject is given 3 months to prepare the speech. With this anticipation period, the TSST takes approximately 15 min. The TSST has been employed in a large number of studies and consistently induces large responses of the stress hormones adrenocorticotropic hormone (ACTH), cortisol, epinephrine and norepinephrine (Kirschbaum *et al.*, 1993).

In all studies, salivary cortisol was measured before and repeatedly after the stress test for up to 90 min post stress. GC sensitivity was measured by LPS-stimulation of whole blood cultures for 6 or 18 h and coincubation of these cultures with different concentrations of DEX and subsequent determination of the pro-inflammatory cytokines IL-6 and TNF-α in the plasma. To obtain an easy to read index of GC sensitivity, the "inhibitory concentration 50%" (IC_{50}) of the dose-response curve of DEX suppression of cytokine production was calculated, which is inversely related to GC sensitivity. The target

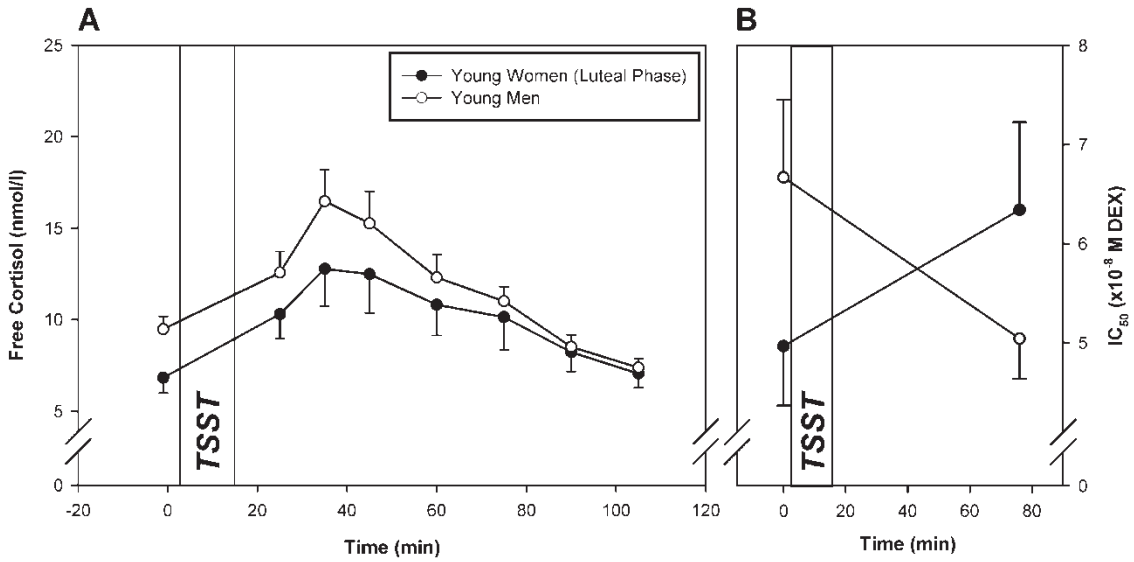

FIGURE 3 (A) Salivary cortisol response and (B) response of dexamethasone sensitivity of lipopolysaccharide induced cytokine secretion in whole blood of healthy young women ($n = 18$) and men ($n = 27$) after psychosocial stress. The bar labeled "TSST" indicates exposure to psychosocial stress. The IC_{50} shown here is inversely related to sensitivity of cytokine secretion to inhibition by dexamethasone, i.e. a high IC_{50} indicates a low sensitivity and vice versa. The post-stress increase in dexamethasone sensitivity in the men is significant (see text).

tissue studied with this GC sensitivity paradigm is the so-called first defense line of the immune system or the inflammatory response. By using the synthetic GC DEX, some of the mechanisms of GC signal transduction, such as binding to MR do not play a role in the model. Since we use unseparated whole blood, the complex cellular network of the immune system remains intact and cellular stress due to the separation process and handling of the sample is reduced (Elenkov *et al.*, 2001).

Sex Differences in the GC Sensitivity Stress Response

We first studied differences in GC sensitivity between healthy young women and men. We set out to find (a) whether women and men differed in their GC sensitivity at baseline and (b) whether an acute and single exposure to psychosocial stress and the associated increase in stress hormone secretion could induce measurable changes in GC sensitivity, as was earlier shown for acute exposure to exercise (DeRijk *et al.*, 1996). We investigated 18 women in the luteal phase of the menstrual cycle and 27 men, both with a mean age of 25 years and a mean body mass index of 22 kg/m^2. As expected, exposure to the TSST induced significant increases in free cortisol measured in saliva in both groups of subjects with no significant group differences (time effect: $F_{2.36,87.36} = 21.60$, $p < 0.001$; group by time interaction: $F_{7,259} = 1.16$, $p = 0.32$).

GC sensitivity was measured directly before and one hour after the end of the TSST. The dose-response curves of DEX inhibition of LPS-induced IL-6 production showed the following: before stress, men and women had similar plateau levels of IL-6 production with low levels of DEX, indicating that stimulated cytokine production was not different at baseline. However, the slopes of the dose-response curves were different between the sexes, which was also shown by the IC_{50} values. At baseline women had a significantly higher GC sensitivity than men. Interestingly, one hour after the stress test, stimulated IL-6 secretion had significantly decreased in the men, while remaining unchanged in the women (sex by time interaction: $F_{1,38} = 4.98$, $p < 0.05$). Accordingly, the IC_{50} showed that GC sensitivity had increased significantly in men, while in women, a slight decrease was observed, which failed to reach statistical significance ($F_{1,42} = 5.44$, $p < 0.05$; see Fig. 3) (Rohleder *et al.*, 2001).

Thus this first study we showed that the GC sensitivity of the inflammatory response system or first-defense line of the immune system seems to differ between men and women, and can be rapidly changed in response to stress.

Age and Sex-steroid Related Differences in GC Sensitivity

In a second study, we investigated the impact of age on GC sensitivity. Aging is associated with profound changes in the endocrine and immune systems, which are hypothesized to be interrelated (Straub *et al.*, 2000). Therefore, we employed the same paradigm as in the first study, but investigated healthy elderly men ($n = 14$; mean age 67.27 years) and again healthy young men as controls ($n = 14$; 25.25 years). In addition, since the results of the first study pointed to a role of sex steroids in influencing GC sensitivity, we investigated a further group of healthy elderly men, who received a testosterone injection five days before the experiment ($n = 12$; 68.69 years).

Total and free plasma testosterone, as well as estradiol levels were significantly higher in young and testosterone treated elderly, compared to untreated elderly subjects (all $p < 0.01$). After stress, total plasma and salivary

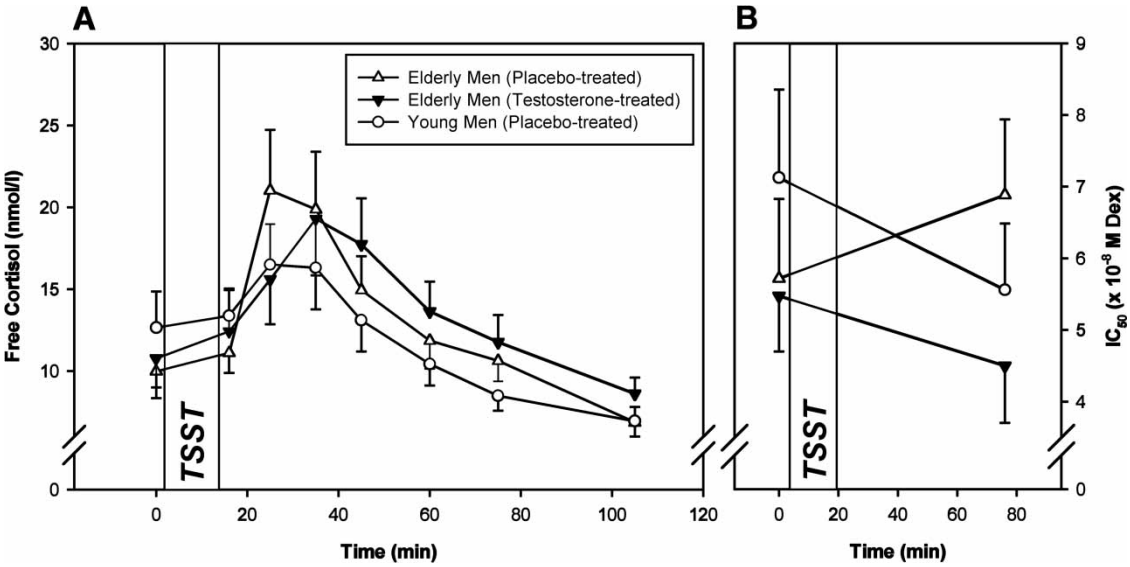

FIGURE 4 (A) Salivary cortisol response and (B) response of dexamethasone sensitivity of lipopolysaccharide induced cytokine secretion after psychosocial stress in whole blood of testosterone- ($n = 14$) and placebo-treated ($n = 12$) elderly men and young men ($n = 14$). The bar labeled "TSST" indicates exposure to psychosocial stress. The IC_{50} shown here is inversely related to sensitivity of cytokine secretion to inhibition by dexamethasone, i.e. a high IC_{50} indicates a low sensitivity and vice versa. The post-stress increase in dexamethasone sensitivity in the young men and elderly men treated with testosterone is significant (see text).

free cortisol levels increased significantly in all groups, while no differences could be observed between the groups (time effect, plasma cortisol: $F_{1.47,98.67} = 4.15$, $p < 0.01$; salivary cortisol: $F_{1.74,62.55} = 7.13$, $p < 0.01$, group by time interaction: both $p > 0.05$). LPS-stimulated cytokine production was lower in untreated elderly subjects compared to the other groups with higher testosterone and estradiol levels ($F_{2,37} = 2.58$, $p = 0.09$).

GC sensitivity as indexed by the IC_{50} of the dose-response curves showed a significant group by time interaction: the increase in GC sensitivity of young subjects after stress was replicated in this study. In contrast, elderly subjects not treated with testosterone showed a slight but not significant decrease, while testosterone-treated elderly men showed the same pattern as healthy young men: an increase of GC sensitivity in response to stress (group by time interaction: $F_{2,37} = 5.28$, $p < 0.01$; see Fig. 4) (Rohleder *et al.*, 2002).

In summary, this second study confirmed that GC sensitivity could be rapidly modulated by acute stress. Furthermore it was shown that aging is accompanied by changes in GC sensitivity and that these changes may be associated with sex steroid levels, since testosterone substitution restored a "young" response pattern.

Impact of Oral Contraceptives on GC Sensitivity

To further explore the role of sex steroids in the altered GC sensitivity in response to psychosocial stress, we investigated in a third study women using oral contraceptives. This is especially interesting as these women show decreased free cortisol responses to stress (Kirschbaum *et al.*, 1999). If free GC levels are important in terminating immune responses after stress, as proposed by Munck *et al.* (1984) then women using oral contraceptives with their low cortisol levels after stress should be subjected to greater allostatic load, if not, then the decreased cortisol levels are expected to be compensated by an increased sensitivity at the level of the target tissues. Using the same experimental protocol, i.e. the TSST with repeated measurement of cortisol before and after stress, we investigated 14 women on oral contraceptive medication (mean age 25.18 years) and 11 women in the luteal phase of the menstrual cycle as a control group (mean age 22.62 years).

As expected from earlier studies, the TSST induced significant increases in free cortisol only in the group of unmedicated women. The women on oral contraceptive medication had a blunted cortisol response, which was significantly lower than that of the healthy controls (group by time interaction: $F_{2.97,65.34} = 4.58$, $p < 0.01$). LPS-stimulated production of IL-6 and GC sensitivity was measured three times in this experiment: directly before, as well as 10 and 60 min after stress. Cytokine production significantly decreased 10 min after stress in luteal phase women and returned to baseline one hour after stress. Cytokine levels of oral contraceptive users just increased slightly during the time of the study ($F_{1.16,20.83} = 5.61$, $p < 0.05$). Large group differences were found for GC sensitivity: while luteal phase women again showed a slight but non-significant decrease, women using oral contraceptives showed a response pattern similar to that of healthy young men. GC sensitivity in oral contraceptive users increased significantly after the stress

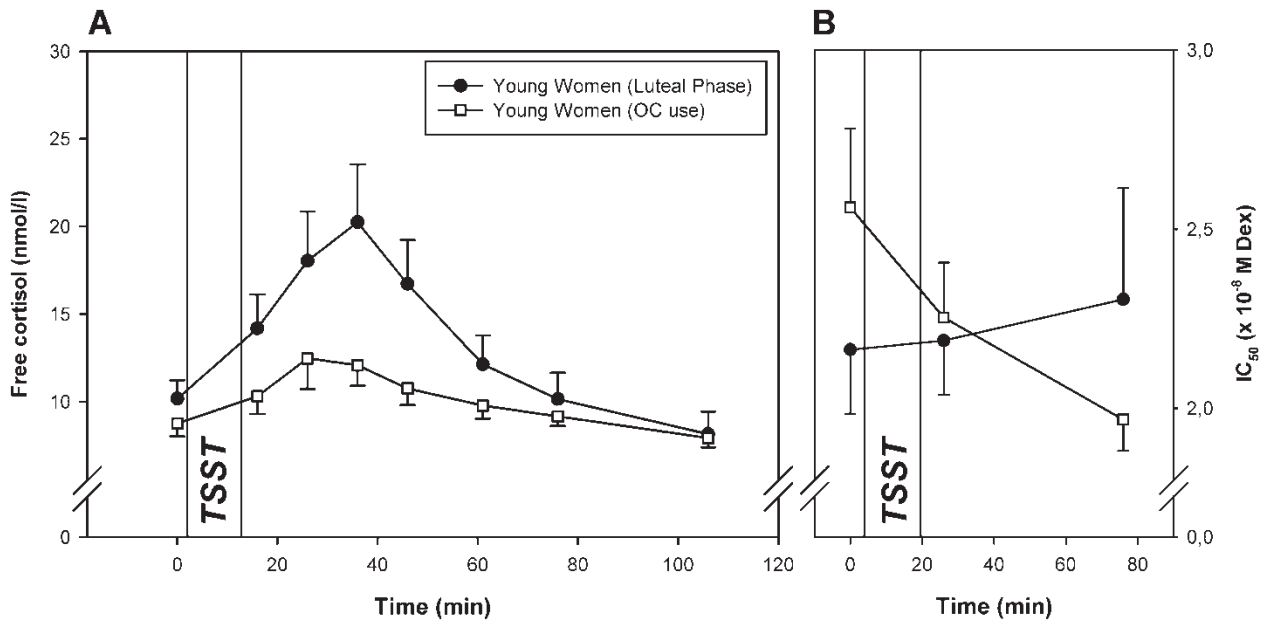

FIGURE 5 (A) Salivary cortisol response and (B) response of dexamethasone sensitivity of lipopolysaccharide induced cytokine secretion after psychosocial stress in whole blood of young women with ($n = 14$) and without ($n = 11$) oral contraceptive medication. The bar labeled with "TSST" indicates exposure to psychosocial stress. The IC_{50} shown here is inversely related to sensitivity of cytokine secretion, i.e. a high IC_{50} indicates a low sensitivity and vice versa. The reduced cortisol response to stress in the women taking oral contraceptive, and their increased dexamethasone sensitivity after stress are significant (see text).

test (group by time interaction: $F_{2,46} = 3.56$, $p < 0.05$, see Fig. 5) (Rohleder *et al.*, 2003).

SUMMARY AND OUTLOOK

Taken together, the studies cited above support the conclusion that GC sensitivity of diverse target tissues can vary between and within individuals. When measured at baseline, age-related differences can be identified, with greater GC sensitivity in very young individuals and decreases with advancing age towards adulthood (Kavelaars *et al.*, 1995); In later life GC sensitivity seems to increase again (Rohleder *et al.*, 2002). Like GC secretion, GC sensitivity may show circadian variations; however, this was found in only one of two studies (Gratsias *et al.*, 2000). GC sensitivity has been investigated in populations with changes in basal HPA axis activity due to clinical disorders. Patients with chronic fatigue syndrome seem to have increased GC sensitivity of different immunological target tissues (Visser *et al.*, 2001a), and patients with depression have decreased GC sensitivities in different tissues (Lowy *et al.*, 1984; Bauer *et al.*, 2003). Repeated and chronic exposure to stress decreases sensitivity of target tissues to GCs (Sauer *et al.*, 1995).

The data from these studies suggest the cautious conclusion that conditions with high cortisol levels are accompanied by decreased GC sensitivity and conditions with low cortisol levels are accompanied by increased target tissue sensitivities. Thus it seems that compensatory mechanisms take place at the level of the target tissues to counteract dysregulated hormone concentrations. However, these mechanisms are presumably not always sufficient to prevent adverse effects in terms of allostatic load. Patients with major depression for example show increased HPA axis activity (Plotsky *et al.*, 1998) and greater susceptibility to infections. This could be the result of decreased efficacy of cell-mediated immunity. Interestingly, these patients also have an increased inflammatory status (Kiecolt-Glaser and Glaser, 2002), indicating that down-regulation of GC sensitivity may be insufficient to prevent high systemic pro-inflammatory cytokine levels. To extend these findings, the GC sensitivity of cell mediated adaptive immunity in depression should be assessed in future studies.

The studies summarized here further show that GC sensitivity not only differs between individuals but is also subject to rather fast modulation in response to physical and psychological stimulation. Interestingly, the differences in the response pattern seem to be associated with sex hormone status and age of the subjects (Rohleder *et al.*, 2001; 2002; 2003). Unfortunately, few studies on potential mechanisms of GC sensitivity modulation have so far focused on the effects of sex steroids. Nevertheless, progesterone for example has been shown to increase the expression of the inhibitory protein IκB-α in cultured mouse macrophages (Miller and Hunt, 1998), which could by decreasing NF-κB activity also influence GC sensitivity. In addition, progesterone binds to the same hormone response element as the activated GR, and by this mechanism progesterone may enhance GR activation of IκB-α, and thereby increase GC sensitivity of cytokine production (Deroo and Archer, 2002). No data are

available on the effects of other sex steroids on GC sensitivity, so the picture is incomplete. Nevertheless, the studies reviewed here show that sex steroids not only influence the activity of the HPA axis (for review see: da Silva, 2002), but also the efficacy of GCs at the level of the target tissue. This finding might help to explain different susceptibilities to chronic inflammatory diseases and infections between men and women.

Data on how potential mediators influence the rapid modulation of GC sensitivity are also sparse. The time course of stress-mediated changes in GC sensitivity implies that stress mediators of the first wave (Sapolsky *et al.*, 2000), such as catecholamines, must be involved in mediating the change in GC sensitivity. One candidate could be norepinephrine, due to its potential to activate the transcription factor NF-κB (Bierhaus *et al.*, 2003), which then would decrease GC sensitivity.

In conclusion, the studies available to date indicate a rather large individual variability of corticosteroid sensitivity in humans, between men and women, old and young people, and even within individuals, in response to physical or psychological stress. It is clear that hypotheses and data on how GC sensitivity is rapidly modulated after stress are scarce. The identification of such mechanisms and potential mediators is clearly a task for the near future. Furthermore, the measurement of GC sensitivity should be extended from healthy subjects to patients with relevant immunological and inflammatory diseases, such as atopic dermatitis, asthma, inflammatory bowel diseases, or rheumatoid arthritis. GC sensitivity should be assessed in more types of target tissues, not only those involved in cellular and humoral immunity, but also those GC target tissues involved in metabolism, reproduction, behavior, or cognition. The findings could be useful to better understand the role of the HPA axis and GCs in the pathophysiology of inflammatory diseases and to identify more precisely targeted treatments.

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