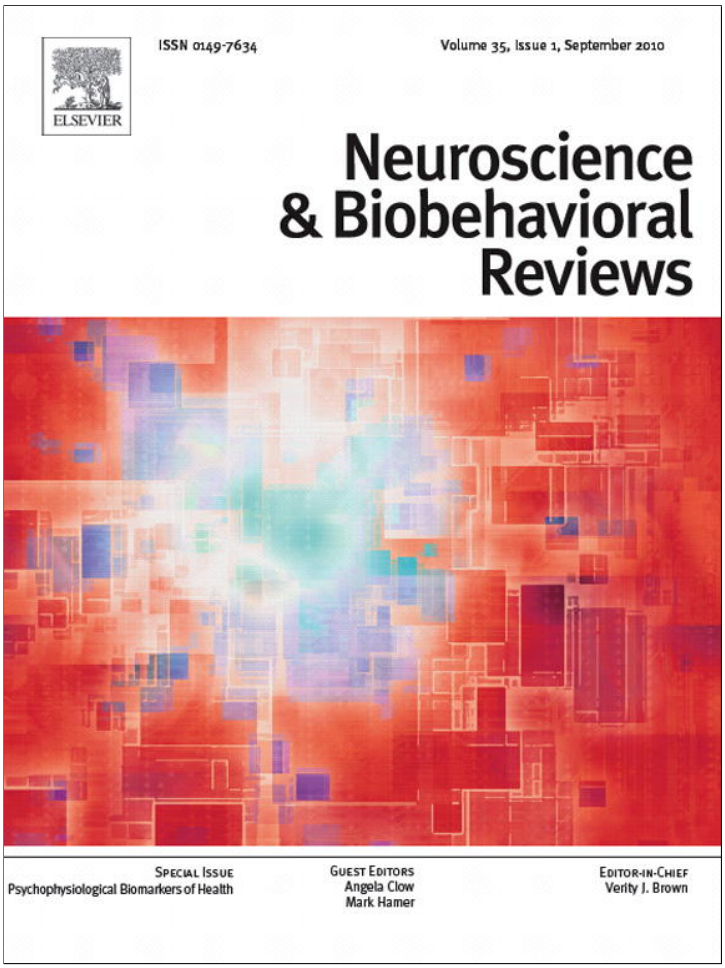

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Review

Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder

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ABSTRACT

Both hyper- and hypo-activity of the hypothalamus–pituitary–adrenal (HPA) axis activity are a consistently reported hallmark feature of stress-related disorders, such as major depression and posttraumatic stress disorder (PTSD), respectively. In this manuscript, however, we are summarizing evidence pointing to altered glucocorticoid (GC) sensitivity in relevant target tissues for HPA axis hormones. Specifically, we provide a summary of GC effects on cognitive functions, as an emerging marker for central nervous system GC sensitivity, and of GC effects on peripheral inflammatory responses. With regard to depression and PTSD, evidence thereby points to decreased GC sensitivity of the cognitive and inflammatory systems in depression, and increased GC sensitivity of both systems in PTSD. Taken together, these data support the hypothesis that both psychiatric disorders are characterized by inefficient GC signaling, although through dysregulations at different levels. Potential underlying pathways and implications are discussed.

Contents

1. Introduction

Glucocorticoids (GC), the end hormones of the hypothalamus–pituitary–adrenal (HPA) axis, play a major role in human health and disease. Traditionally, excess secretion of GCs has been viewed as an important factor in immune suppression, the metabolic syndrome, and stress-related psychiatric disorders (e.g. Sapolsky et al., 1986). However, given the importance of sufficient GC

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concentrations for the regulatory control of damaging forces, mainly the inflammatory response system, as well as reports of hypocortisolism in some psychiatric conditions and during chronic stress, deficient GC signaling recently has received increasing attention (e.g. Raison and Miller, 2003; Fries et al., 2005; Heim et al., 2000).

In this review, we will investigate data on the efficiency of glucocorticoid signaling within two target systems that are of particular importance for health and well-being in stress-related psychiatric diseases, specifically in depression and posttraumatic stress disorder (PTSD). One of these target systems is the innate immune system, more specifically the inflammatory cascade, because of its central role in a large number of diseases (e.g. cardiovascular and metabolic diseases (Hansson and Libby, 2006; Hotamisligil, 2006). The second glucocorticoid responsive functional area reviewed here is the central nervous system, more specifically brain regions involved in cognitive processes, like the limbic system and the prefrontal cortex (Lupien et al., 2009; Wolf, 2009).

We will describe possible associations or dissociations of these two systems' glucocorticoid sensitivities and the relevance for human health. Furthermore, evidence for enhanced GC sensitivity in PTSD and reduced GC sensitivity in depression will be discussed. Moreover, possible underlying mechanisms will be briefly highlighted, before a conclusion and a look into the future of this rapidly growing research area is presented.

2. Regulation of glucocorticoid sensitivity in target tissues

Glucocorticoids mediate their effects by binding to cytosolic receptors, of which two subtypes have been described: The type-1 or mineralocorticoid receptor (MR) and the type-2 or glucocorticoid receptor (GR; de Kloet et al., 2005; McEwen et al., 1997). The two receptors differ in their affinity for cortisol (with the MR having a ten-fold higher affinity). In addition they differ in their localization within the CNS and in the periphery (Miller et al., 1990). Although both receptors reside in the cytoplasm, recent evidence suggests the existence of a membrane bound form of the MR characterized by a lower affinity compared to its intracellular counterpart (Joels et al., 2008). Since the MR appears to have a limited role in the influence of GCs on the immune system (Lim et al., 2007), and due to the fact that most CNS effects of increased GCs on memory have been attributed to GR mediated effects (Roozendaal et al., 2006) we focus on the GR in this review. However, preliminary evidence pointing to involvement of the MR in the processes described in the following will be presented.

Generally, the GR is found in the cytoplasm as part of an assembly consisting of the receptor itself, the chaperones heat shock protein 90 (HSP90), HSP70, as well as co-chaperones, such as FK506 binding protein 5 (FKBP5), and other proteins, such as p23 (Pratt, 1993). This GR heterocomplex undergoes constant conversion from a non-steroid binding back to a steroid binding state. Upon ligand binding, the GR dissociates from the chaperone protein complex, undergoes a conformational change, and translocates to the nucleus. Within the nucleus, hormone-activated GR homodimers can act in two ways, either by interacting with specific DNA sequences (glucocorticoid response elements, GREs) in the promoter region of glucocorticoid responsive genes, thereby enhancing (GRE) or inhibiting (negative GRE, nGRE) transcription, or by interaction with other transcription factors (McKay and Cidlowski, 1999). Given the complexity of the glucocorticoid signal transduction pathway, it is conceivable to expect various mechanisms and modulators to interfere at different levels and thus to change the transcriptional output (for an overview, see Bamberger et al., 1996). For example, GR number and function can be regulated ligand-dependently, by the concentration of GCs themselves (Silva et al., 1994), or ligand-independently, by factors such as pro-inflammatory and type-1 cytokines that are found to up-regulate transcription of the GR (e.g. Pariante et al., 1999). One pathway might be the specific up-regulation of the non-ligand-binding beta isoform of the GR (GR-beta), which is thought to act as an endogenous inhibitor of GC action (Bamberger et al., 1995; Webster et al., 2001) resulting in the down-regulation of glucocorticoid sensitivity of target cells (for more details on cytokine effects on GR function, see Pace et al., 2007).

Given the number of steps and the plethora of already documented, as well as probably yet undiscovered influences on the GC signaling cascade, it is not surprising that studies conducted in the last decade were able to report inter- and intra-individual differences in the ability of target tissues to respond to glucocorticoid signals (DeRijk et al., 1996; Miller et al., 2002a; Rohleder et al., 2003). Furthermore, some of these factors are constant within one organism (e.g. GR polymorphisms), while others can differ between target tissues. Some modifications of the signaling cascade are dynamic, for example, leading to GC sensitivity alterations during acute stress (Rohleder et al., 2003), while others can be better described as relatively static or as long-term alterations, for example, due to early life experiences or chronic stress (e.g. Miller et al., 2002a; Weaver et al., 2004; Rohleder et al., 2009a). Because of the potential variability of different target tissues' sensitivity to vital GC signaling, it has been concluded that assessment of GC concentrations alone is not sufficient to draw conclusions about the efficiency of HPA signaling. Hence, in the following two sections, we will describe methods to assess glucocorticoid sensitivity in two tissues, the central nervous system (CNS) and the immune system.

2.1. Assessment of glucocorticoid sensitivity in CNS structures relevant for cognition

With regard to the CNS, electrophysiological measures have been used to investigate central GC sensitivity in animals (e.g. in vitro changes in neuronal excitability in hippocampal slices; Diamond et al., 2007; Joels, 2001). However, in humans, such invasive approaches are not feasible. Hence, human research has to address the issue of central GC sensitivity via indirect approaches.

One approach is to utilize GCs, negative feedback action on the pituitary and the hypothalamus (Dallman et al., 1994; de Kloet et al., 2005). The sensitivity of these target regions can be assessed using well-established pharmacological challenge protocols such as the dexamethasone (DEX) suppression test (DST; The APA Task Force on Laboratory Tests in Psychiatry, 1987) or the combined DEX/CRH Test (Ising et al., 2005). The DST primarily tests feedback at the level of the pituitary (de Kloet, 1997), while the DEX/CRH test might assess feedback sensitivity of supra hypothalamic regions (Ising et al., 2005).

GCs also act on a range of other brain structures that are involved in HPA control, but are also crucially important for learning and memory. In this context, the hippocampus, the amygdala, and the prefrontal regions have received attention (de Kloet et al., 2005; Diamond et al., 2007; Joels et al., 2006; Wolf, 2008). For hippocampus mediated long-term memory, GCs enhance memory consolidation but impair memory retrieval. These behavioral effects are caused by GC effects on neurons in the amygdala and hippocampus (Joels et al., 2006; Roozendaal et al., 2006; Wolf, 2009). In addition, there is evidence that GCs impair cognitive functions mediated by the prefrontal cortex (e.g. working memory; Lupien et al., 1999).

Experimental studies investigating central nervous system effects of GCs regularly observe a substantial inter-individual variation in the size of the GC effect on memory. This variation

might be caused by modulatory state influences like motivation, arousal, test anxiety, and the time of day (see Lupien et al., 2007; Wolf, 2008, 2009), but another interpretation might be that inter-individual variations in GC sensitivity are responsible for explaining at least a part of this variance. Thus we suggest that the effects of GC administration on memory can be used as an indirect behavioral measure of central GC sensitivity. In such studies the behavioral performance after GC administration has to be compared to the performance after placebo administration using a double blind design (e.g. Rohleder et al., 2009b; Schlosser et al., 2009). Specific brain regions can be investigated indirectly by choosing cognitive tasks known to rely on the brain region of interest. For example, a working memory task might be used to assess GC sensitivity of the PFC (e.g. Lupien et al., 1999). Similarly, delayed retrieval could be used in order to assess GC sensitivity of the hippocampus (e.g. de Quervain et al., 2000; Kuhlmann et al., 2005). We suggest that for the assessment of central GC sensitivity, acute single administrations of the natural human GC cortisol are most ecologically valid. Such a treatment does, of course, not allow a differentiation of the role of the two receptors (MR and GR) in mediating the observed behavioral effects. Follow up studies might thus use specific agonists or antagonists in order to characterize the role of each receptor in more detail (e.g. Otte et al., 2007, 2009).

Another approach for the assessment of central GC sensitivity consists of using neuroimaging techniques. For example, acute effects of GCs could be investigated using PET, fMRI, or EEG (e.g. Yehuda et al., 2009b). The major advantage in this regard would be to not having to rely on indirect evidence derived from neuropsychological tests, while disadvantages are costs, availability, and sometimes unclear relationship to overt behavior.

2.2. Assessment of glucocorticoid sensitivity of peripheral inflammatory pathways

Glucocorticoid sensitivity of the immune system has been assessed relatively early in psychiatric disorders (e.g. Lowy et al., 1984), usually following one of two different approaches: One involves in vivo testing of immune responses after systemic GC application and interpreting the relative response of the immune measure as glucocorticoid sensitivity (e.g. Bauer et al., 2002). An advantage of this approach is the assessment of systemic responses that can be directly related to other parameters, such as HPA feedback sensitivity. An alternative approach is to assess GC sensitivity in vitro, by adding GCs to functional tests in culture. Typically, whole blood or separated mononuclear cells are incubated with immune activating mitogens in several different aliquots, while each of those aliquots is co-incubated with a different concentration of GCs. After incubation, culture supernatants are harvested and cytokines measured to index immune activation. The resulting dose–response curve can be mathematically reduced to single-number indices, such as the inhibitory concentration 50% (IC50), which represents the respective GC concentration required to suppress immune function by 50% (e.g. Rohleder et al., 2003). Although these methods do not provide real life tests of systemic function, a major advantage is that GC sensitivity can be assessed after experimental immune activation, thus providing information about the glucocorticoids' ability to, for example, control a potentially occurring inflammation without subjecting the patient to any inflammatory stimuli or glucocorticoids.

Within both approaches, it is necessary to select immune functions relevant to the immune function of interest. Most studies assessing GC sensitivity of the inflammatory cascade, for example, have focused on inflammatory cytokines, such as interleukin (IL)-6, IL-1beta, or tumor necrosis factor (TNF)-alpha. Furthermore, the specific GC (endogenous versus synthetic), and the route of application need to be carefully selected. While earlier studies have employed the synthetic GC dexamethasone (e.g. DeRijk et al., 1996; Rohleder et al., 2003), newer study protocols have used the endogenous GC hydrocortisone (Rohleder et al., 2009a).

Recent advances in technology have lead to the introduction of additional ways to assess GC sensitivity. Cole et al. (2007) describe a method in which genomewide RNA expression of peripheral blood mononuclear cells is measured with microarrays, and the resulting data is interpreted in terms of upstream signal transduction pathways stimulating expression of the specific gene products. To assess the efficiency of the glucocorticoid signaling pathway, the relative number of genes being regulated by glucocorticoid response elements (GRE) can be quantified, and compared with genes regulated by inflammatory or other signaling pathways (Cole et al., 2007). Using this innovative approach, Miller et al. (2008) have shown diminished GR signaling, indicative of lower GC sensitivity in individuals suffering from chronic stress. No studies have yet applied this methodology to patients with posttraumatic stress disorder or depression, however future studies using this approach will greatly advance our understanding of GC signaling pathways in these and other stress-related disorders.

3. Glucocorticoid sensitivity in depression and posttraumatic stress disorder

GC sensitivity has repeatedly been implicated to play an important role in stress-related psychiatric diseases, specifically in depression and posttraumatic stress disorder (PTSD; e.g. Raison and Miller, 2003). In the following, we will summarize data on central and immune GC sensitivity in these two disorders.

3.1. Depression

A major depressive episode is characterized by depressed mood and loss of interest. Furthermore, changes in psychomotor activity and sleep disturbances as well as recurrent circular negative thoughts are common (American Psychiatric Association, 1994). In addition, patients suffer from a range of cognitive and health problems, both of which seem to be affected by glucocorticoid signaling. Typical HPA axis dysregulations include increased central CRH activity, associated with higher peripheral cortisol concentrations (Nemeroff, 1996), and reduced negative feedback sensitivity, as shown by DST non-suppression and an exaggerated response to the DEX/CRH test (Ising et al., 2005; The APA Task Force on Laboratory Tests in Psychiatry, 1987).

3.1.1. Molecular factors regulating glucocorticoid sensitivity in depression

As mentioned above, a wide variety of factors might affect GC effects on target tissues. So far, little evidence links MR polymorphisms with depression. One polymorphism potentially interesting is the MR polymorphism I180V, as it was associated with enhanced cortisol secretion during acute psychosocial stress and reduced cortisol-ligand function (DeRijk et al., 2006). In accordance with these findings, one study reported higher prevalence of depressive symptoms in I180V-allele carriers compared to non-carriers (Kuningas et al., 2007). Contrary to the MR, however, GR polymorphisms, specifically the two polymorphisms of the GR gene BclI (an intronic C to G nucleotide change) and ER22/23EK (two linked nucleotide changes in codons 22 and 23, one silent (both coding for glutamic acid (E)), one resulting in a change from arginine (R) to lysine (K)), have received increasing attention. In healthy individuals, the BclI G-allele was found to be associated with hypersensitivity to GCs determined by lower cortisol levels in response to DEX and low dose DST in G-allele carriers (GG < CG)

compared to CC-carriers (van Rossum et al., 2003), while ER22/23EK has been associated with GC resistance as assessed by higher cortisol levels in response to 1 mg-DEX in ER22/23EK carriers compared to non-carriers (van Rossum et al., 2002). Interestingly, despite these opposite effects in healthy individuals, both polymorphisms have been associated with depression. With regard to the ER22/23EK polymorphism, carriers of the less frequent allele were shown to be at higher risk of recurrent depression while at the same time, they also showed a faster clinical response to antidepressant therapy (van Rossum et al., 2006; van West et al., 2006). Carriers of the BclI GG genotype, however, were not only found to be at higher risk of developing a major depressive episode, but the BclI polymorphism also tended to be associated with worse treatment outcome as well as in some studies, with higher ACTH levels in the DEX/CRH test, especially in homozygous (GG) patients (van Rossum et al., 2006; Brouwer et al., 2006). It has been speculated that one reason for these contradictory findings may be that the BclI polymorphism exerts its effect in a tissue and brain region specific manner, while GC resistance in ER22/23EK carriers may have 'primed' alternative GC attenuating pathways and as a result allows for faster treatment responses (van Rossum et al., 2006). However, as mentioned earlier, the GR is also part of a larger assembly and one important chaperone HSP70, has been implicated as possible modulator of GC signaling in depression. A 162-base deletion in HSP70 mRNA was reported to be specific to patients with major depression (Shimizu et al., 1996). However, a more recent study was not able to support this notion (Takimoto et al., 2003). Nevertheless, Pae et al. (2007) tested five SNPs within the HSP70 family and found one haplotype (T-G-G: rs2227956, rs2075799, rs1043618) within the two genes HSPA1L and HSPA1A to be associated with a poorer response to antidepressants.

Although no human studies are currently linking depression and HSP90, the HSP90 co-chaperone FKBP5 has recently received increasing attention. In more detail, during maturation of the GR complex, FKBP5 binds to HSP90, and as such, FKBP5 is part of the mature GR heterocomplex (Pratt et al., 2006; Schiene-Fischer and Yu, 2001). However, on hormone binding, FKBP5 is replaced by FKBP4, allowing nuclear translocation and transcriptional activity (Davies et al., 2002; Wochnik et al., 2005). FKBP5 binding results not only in a lower affinity of the receptor complex for cortisol, FBKP5 has also been shown to promote nuclear translocation of the non-active beta-isoform of the GR, thereby further decreasing overall GR signaling (Zhang et al., 2008). Lastly, GR sensitivity is additionally regulated by GCs inducing the expression of FKBP5, thereby constituting an intracellular ultra-short negative feedback loop (Hubler and Scammell, 2004; Vermeer et al., 2003). Given these roles of FKBP5 in GR signaling, it can be hypothesized that increased expression of FKBP5 would lead to reduced GC sensitivity or GR resistance. This hypothesis is substantiated by findings linking over-expression of FKBP5 to relative GC resistance and high cortisol levels in squirrel monkeys (Denny et al., 2000; Reynolds et al., 1999; Westberry et al., 2006) and furthermore, by a study connecting FKBP5 SNPs (minor alleles of rs4713916, rs1360780, and rs3800373) associated with increased FKBP5 protein to incomplete recovery of cortisol stress responses (Ising et al., 2008). In line with these findings, Binder et al. (2004) found patients suffering from depression and homozygous for the minor allele (TT) at rs1360780 to not only to have more than twice as many depressive episodes, but also to show a faster response to antidepressant drugs. Although the presence of the rs1360780 TT genotype itself could not be linked to enhanced circulating cortisol levels, a stronger correlation between cortisol and FKBP5 mRNA in this genotype as well as lower ACTH responses to the DEX/CRH test in those patients suggested a counter-regulatory effect on depression-related HPA axis hyperactivity. Or in other words, in parallel to ER22/23EK, the FKBP5 polymorphism rs1360780 (TT) may be associated with GC resistance and depression, but at the same may also allow for alternative regulatory pathways. However, while data from several other studies support these findings, they also at the same time caution against generalization. For example, in another German sample, FKBP5 variants rs3800373 and rs1360780 were again linked to a higher chance to respond to antidepressant drug treatment (Kirchheiner et al., 2008) and Lekman et al. (2008) found an association between the rs1360780 TC-heterozygous genotype and depression in White non-Hispanic but not in a Black population as well as an association between the A-allele of rs4713916 and remission response in all groups investigated. However, this latter effect was again mainly driven by the White non-Hispanic population. Interestingly, the T-allele of FKBP5 SNP rs1360780 was also associated with a lack of treatment response in a Spanish population (Papiol et al., 2007), and in a Chinese population (Tsai et al., 2007). Furthermore, Gawlik et al. (2006) did not find any association between depression and several tested FKBP5 polymorphisms, including rs1360780, at all. Lastly, it has to be pointed out that data clarifying the role of FKBP5 in the CNS are scarce, although one study showed increases in FKBP5 at both the transcript and protein levels assessed post-mortem in frontal cortical gray matter of depressive patients (Tatro et al., 2009).

In summary, in the context of depression, many parameters potentially altering GC signaling are not yet sufficiently understood, but several GR and FKBP5 gene polymorphisms have been more consistently implicated in depression then others. Interestingly, two of those polymorphisms (GR: ER22/23EK and FKBP5: T-allele of rs1360780) seem to play a rather complex role, as they are associated with higher symptom severity and faster treatment response (at least in a White non-Hispanic population). Although based on preliminary data, it can be speculated that while these polymorphisms may represent risk factors for developing a dysregulated HPA axis and thus depression on the one hand, they subsequently may also allow for a faster normalization of a dysregulated HPA axis.

3.1.2. *Glucocorticoid sensitivity of cognitive function in depression*

In line with changes in mood, the entire information processing including attention, memory encoding, and retrieval is characterized by a negative bias in depression (e.g. Wolf, 2008). With respect to studies using cognitive paradigms to indirectly measure central GC sensitivity, one of the authors recently demonstrated that in contrast to healthy controls, patients suffering from major

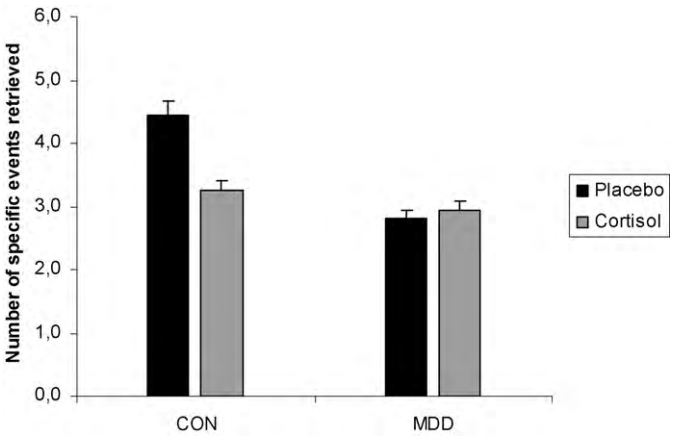

Fig. 1. Evidence for reduced central glucocorticoid sensitivity in major depressive disorder (MDD). While cortisol administration impaired autobiographic memory in healthy controls ($n = 16$), it had no effect on autobiographical memory in patients with MDD ($n = 16$). Taken from Schlosser et al. (2009), reprinted with permission from Elsevier.

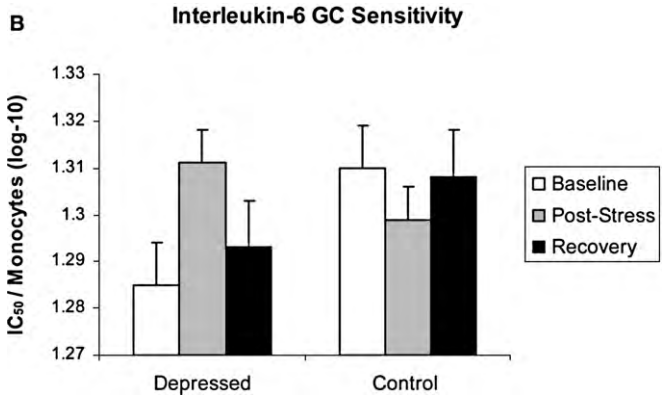

Fig. 2. Acute response of glucocorticoid sensitivity of IL-6 to a laboratory stress paradigm. Shown is the inhibitory concentration 50% (IC_{50}) of the dose–response curve of dexamethasone suppression of mitogen-induced inflammatory mediator (IL-6) production. The lower baseline IC_{50} in clinical depression indicated higher baseline GC sensitivity, while in response to acute stress, depressed participants developed a relative glucocorticoid resistance. Taken from Miller et al. (2005b), reprinted with permission from Wolters Kluwer Health.

depression (MDD) do not show impaired autobiographical memory retrieval after a single cortisol administration (see Fig. 1; Schlosser et al., 2009). This study replicated an impairing effect of GCs on autobiographical memory retrieval as originally reported by Buss et al. (2004). Additionally it is the first to suggest that MDD patients are less responsive to acute GC changes at the level of the central nervous system. Differential effects of repeated DEX administration on memory in patients with MDD compared to healthy controls have been reported in a previous study (Bremner et al., 2004b) even though comparison with our study is somewhat limited by the usage of different GCs and different treatment designs (single acute versus sub-chronic prolonged). As mentioned above we suggest that for the assessment of central GC sensitivity acute single administrations of the natural human GC cortisol are most ecologically valid. In summary the study mentioned above (Schlosser et al., 2009) provides preliminary evidence for a reduced GC sensitivity of cognitive functions in depression.

3.1.3. Glucocorticoid sensitivity of peripheral inflammatory pathways in depression

The inflammatory response system has been identified as a major player in depression. There is compelling cross-sectional evidence that the inflammatory system is up-regulated (e.g. Ford and Erlinger, 2004; Miller et al., 2002b), and recent prospective studies have shown that depression is an antecedent, rather than a consequence of inflammation (e.g. Gimeno et al., 2009; Rohleder and Miller, 2008). Additionally, inflammation has been suggested to be a mediator of heightened risk for cardiovascular disease in depression (Frasure-Smith and Lesperance, 2006). However, in light of increased or normal HPA axis activity, heightened inflammation is not an expected finding given the anti-inflammatory effects of glucocorticoids. Raison and Miller (2003) and others (e.g. Miller and Blackwell, 2006) have proposed that inefficient glucocorticoid signaling, characterized by reduced glucocorticoid impact on immune target tissues, might be permitting inflammatory disinhibition. Indeed, inefficient GC signaling in the form of lower HPA axis feedback seems to be a key feature of depression, but is there evidence for altered GC sensitivity in the immune system, specifically, the inflammatory cascade?

Glucocorticoid receptor function in depression was first investigated by Lowy et al. (1984), who found that while control participants' in vitro lymphocyte proliferation was markedly reduced after oral GC, only a small percentage of depressive patients' lymphocytes were GC responsive (Lowy et al., 1984). More recently, two reviews of studies investigating GR number and function in Major Depression concluded that while GR numbers seem to be comparable between patients and controls in most studies, functional studies showed clear evidence for reduced GC sensitivity (Pariante and Miller, 2001; Pariante, 2004). Only three additional studies have investigated the association of GC sensitivity of inflammatory parameters with depression since then. Miller et al. (2005a) report higher inflammatory GC sensitivity in a sample of coronary heart disease patients with depressive symptoms. Similarly, higher baseline GC sensitivity was found in a sample of participants with clinical depression in comparison with control participants (Miller et al., 2005b). However, when subjected to acute psychosocial stress, depressed participants developed a relative GC resistance (Miller et al., 2005b, see Fig. 2). This latter finding shows that stress system activation might be necessary to reveal alterations of GC signaling pathways. Finally, a study by Carvalho et al. (2008) did not report alterations in GC sensitivity of LPS-stimulated IL-6 production of a group of patients with treatment resistant depression, but their study revealed a more complex dysregulation; in contrast to healthy controls, co-incubation of patients' blood with the antidepressant clomipramine did not modulate the in vitro effects of GC's on inflammation (Carvalho et al., 2008).

In summary, while more general tests of immune function clearly support the notion of reduced GC sensitivity in depression, recent studies specifically testing inflammatory GC sensitivity point to a more complex regulation.

3.2. Posttraumatic stress disorder

Posttraumatic stress disorder is characterized by re-experiencing, avoidance and hyper arousal (American Psychiatric Association, 1994). Similar to depression, patients suffer from a range of cognitive and health problems in addition to the typical cluster of symptoms, both of which seem to be affected by glucocorticoid signaling. Similarly to depression, HPA axis dysregulation is characteristic of PTSD. Studies of veteran soldiers and civil war victims revealed a pattern characterized by hypo-activity of the HPA axis, altered diurnal rhythms, and stronger cortisol suppression after oral GC administration (e.g. de Kloet et al., 2006; Yehuda et al., 2005). However, the notion of HPA axis hypo-activity is not a uniform finding. For example, increased salivary cortisol was found in intimate partner violence victims with PTSD (Inslicht et al., 2006), and HPA axis feedback sensitivity was reported unaltered in PTSD patients from a community sample (Lindley et al., 2004). Reasons for these and other inconsistent findings might be factors such as type of trauma, sample population, comorbidity with depression, and/or duration between trauma and study participation (e.g. Campbell et al., 2007; Miller et al., 2007; Wessa and Rohleder, 2007).

3.2.1. Molecular factors regulating glucocorticoid sensitivity in PTSD

Various factors involved in the GC signaling pathway may contribute to altered GC sensitivity in PTSD, however, studies are fewer than for depression. We are aware of no study linking MR polymorphisms to PTSD and only one study that found an association between GR polymorphisms and PTSD. However, in this study, although the BclI GG-genotype was associated with low basal cortisol levels in Vietnam veterans with PTSD, it was not more frequent in PTSD patients than in controls, and the PTSD group did not display GC hypersensitivity, making it difficult to draw conclusions (Bachmann et al., 2005).

Although no data were found that allowed us to link PTSD to the GR chaperones HSP70 and HSP90 either, several recent studies suggest a role of the HSP90 co-chaperone FKBP5 in PTSD. For example, a study by Segman et al. (2005) found that the extent of

up-regulation of FKBP5 mRNA only hours after a trauma predicted the development of PTSD (Segman et al., 2005), and Binder et al. (2008) reported that in the presence of severe child abuse, polymorphisms associated with higher induction of FKBP5 and thus GR resistance (rs3800373 CC-genotype, rs1360780 TT-genotype, rs9296158 AA-genotype, and rs9470080 TT genotype) were associated with a higher risk for PTSD (Binder et al., 2008). Two of those polymorphisms (C-allele of rs3800373 and T-allele of rs1360780) had already been linked to peri-traumatic dissociation (a predictor of PTSD) in children after medical trauma (Koenen et al., 2005). On the contrary, low induction alleles (rs3800373: AA; rs9296158: GG; rs1360780: CC; and rs9470080: CC) were associated with relative GR resistance as well as lower symptom severity levels in PTSD patients exposed to childhood trauma, suggesting protective effects of these genotypes (Binder et al., 2008). Interestingly, in the same study, the same polymorphisms associated with increased risk for PTSD were also associated with a higher DEX suppression and thus increased GR sensitivity in PTSD patients (Binder et al., 2008). While increased GR sensitivity is an often-described phenomenon in PTSD, the role of FKBP5 seems to be opposite from what one would expect. However, a recent study by Yehuda et al. (2009a) assessed FKBP5 mRNA levels in PTSD patients and found the expression to be actually reduced rather than enhanced compared to healthy individuals (Yehuda et al., 2009a). This is along the lines of one of our own findings with regard to GC sensitivity of immune processes: while FKBP5 gene expression was not associated with GC sensitivity of IL-6 producing PBMCs in healthy participants, lower FKBP5 levels were associated with enhanced GC sensitivity in Bosnian war refugees with PTSD (unpublished data). These findings support the results of increased GR sensitivity in PTSD patients described by Binder et al. (2008); however, they are still contrary to earlier findings by the same group. However, it has to be pointed out that in the above study, Binder et al. (2008) did not explicitly assess FKBP5 mRNA or protein levels in PTSD patients, but rather inferred enhanced FKBP5 expression (protein levels or mRNA induction by cortisol) and GR resistance from earlier findings in healthy participants (Binder et al., 2004). Likewise, in the study by Yehuda et al. (2009a) and our own study, FKBP5 gene expression but not polymorphisms were assessed. It therefore remains to be shown whether specific FKBP5 genotypes relate to FKBP5 mRNA expression and protein levels in PTSD patients in the same manner as they do in healthy individuals.

However, based on the findings available so far and considering a time perspective, it can be speculated that before exposure to trauma(s), specific FKBP5 polymorphisms may represent a risk factor for the development of PTSD due to GR resistance and thus chronically elevated/prolonged acute stress responses, while at later stages and as a result of trauma exposure(s), exaggerated counter-regulatory processes may come into play resulting in the often observed enhanced GC sensitivity and its negative health effects.

3.2.2. Glucocorticoid sensitivity of cognitive functions in posttraumatic stress disorder

With regard to cognitive functions, current models of PTSD suggest enhanced amygdala reactivity resulting in exaggerated fear memory trace and missing context sensitivity of the conditioned fear response due to hippocampal dysfunction. In addition, prefrontal deficits could be involved in the failure to extinct traumatic memory. An additional role of a dysfunctional hippocampus has been suggested for the distorted explicit memory of the trauma and the often-missing integration of the trauma into autobiographical memory (for a summary, see Wolf, 2008).

Four studies looked at 'central' GC sensitivity by investigating the effects of glucocorticoid treatment on learning and memory tasks in PTSD. One reported stronger negative effects of cortisol on hippocampus-dependent declarative memory in PTSD. In addition, only in PTSD patients did the glucocorticoid lead to impairments in working memory (Grossman et al., 2006). A similar study conducted in older PTSD patients also reported evidence for an enhanced GC sensitivity of the patients for the domain of working memory, however, in this experiment beneficial rather than detrimental effects were observed (Yehuda et al., 2007). In another experiment conducted with younger patients, a more pronounced effect of cortisol on hippocampal-dependent trace conditioning was found (Vythilingam et al., 2006). As shown in Fig. 3, PTSD patients, but not controls, showed impairment after cortisol treatment. Thus all three acute challenge studies support the hypothesis of higher central (hippocampal and potentially also prefrontal) GC sensitivity in PTSD. In contrast to that, Bremner et al. (2004a) reported blunted effects of prolonged dexamethasone treatment on declarative memory in PTSD. Again, similar to the findings in MDD, the latter study is difficult to interpret due to the prolonged administration of a synthetic GC. A recent fluorodeoxyglucose PET study tested central GC sensitivity of PTSD patients compared to controls (Yehuda et al., 2009b). The complex results indicated that the effects of the GC on the nucleus accumbens (ACC), the amygdala and the hippocampus differed substantially between the two groups not only in its quantity but also in its quality (direction and lateralization). However, in summary, current findings support our preliminary hypothesis of increased central sensitivity to single-dose GC application in PTSD.

3.2.3. Glucocorticoid sensitivity of peripheral inflammatory pathways in posttraumatic stress disorder

Similar to depression, over-activity of the innate immune system has been described in PTSD, as recently reviewed (Wessa and Rohleder, 2007). Newer studies continue to replicate this finding (e.g., Hoge et al., 2009; Spitzer et al., 2009). Several authors have suggested that peripheral inflammation is one of the factors underlying the heightened rate of somatic diseases in PTSD (for example Rohleder and Karl, 2006; Spitzer et al., 2009), a hypothesis supported with regard to cardiovascular disease by a recent meta-analytic study (Gander and von Kanel, 2006).

Inflammatory disinhibition is – in contrast to depression – not an unexpected finding in PTSD, if HPA axis dysregulations are taken into account. Early studies have quantified the number of GRs on peripheral blood mononuclear cells (PBMC) and in contrast to depression, most of these studies revealed higher numbers of GRs on PBMCs of PTSD patients (Vidovic et al., 2007; Yehuda et al.,

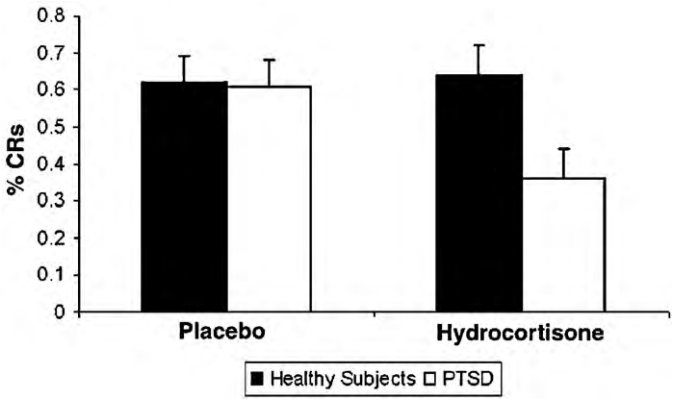

Fig. 3. Evidence for enhanced central GC sensitivity in PTSD patients. While cortisol treatment had no effects on hippocampal mediated trace conditioning in healthy subjects, this function was significantly impaired in patients with PTSD. The figure shows mean conditioned response (CR) averaged over seven acquisition blocks. Taken from Vythilingam et al. (2006), reprinted with permission from Nature Publishing Group.

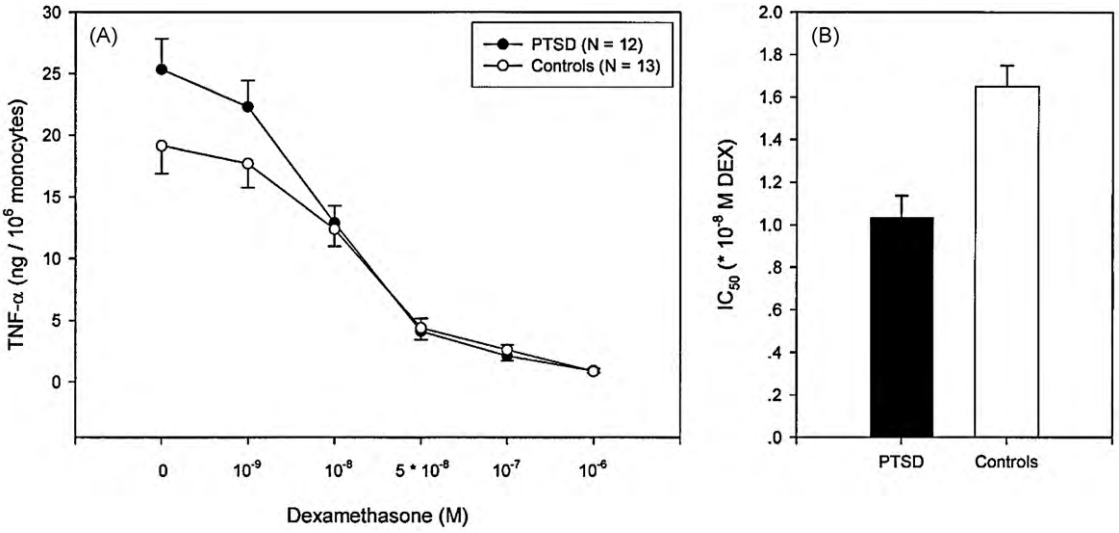

Fig. 4. Glucocorticoid sensitivity of mitogen-stimulated inflammatory cytokine (TNF-alpha) production in vitro. (A) Stimulated TNF-alpha production and dose-dependent GC suppression in Civil War refugees with PTSD and controls. This figure shows a higher inflammatory response in PTSD, in addition to a more efficient regulation by GCs. (B) Inhibitory concentration 50% (IC_{50}) of the dose–response curve. The lower IC_{50} in PTSD patients signifies a higher GC. Taken from Rohleder et al. (2004), reprinted with permission from Elsevier.

1991, 1993). Furthermore, after oral DEX, GR numbers displayed a stronger decrease in PTSD patients compared to controls (Yehuda et al., 1995, 2002). These latter findings are in line with the expected heightened glucocorticoid sensitivity in PTSD. But do these findings translate to a better glucocorticoid regulation of the inflammatory response?

Yehuda et al. (2004, 2006) repeatedly found that glucocorticoid sensitivity of PBMC lysozyme secretion, a direct measurement of innate immune competence, was higher in PTSD patients compared to controls in several studies. Only two studies have quantified in vitro glucocorticoid sensitivity of inflammatory cytokine production in PTSD. In our study, Civil War refugees with PTSD showed hypocortisolism concurrently with increased stimulated cytokine production and increased GC sensitivity of inflammatory cytokine production (see Fig. 4; Rohleder et al., 2004). In contrast to that, de Kloet et al. (2007) reported lower stimulated inflammatory cytokine production, lower GR density, no differences in basal cortisol, and in inflammatory GC sensitivity in PTSD. These divergent findings might be explained by more recent trauma exposure, or by the high rate of comorbid depression in the latter sample. Taken together, current data support the notion of altered GC sensitivity of immune functions in PTSD. However, there is inconsistency in findings related to inflammatory regulation, which might be caused by differences between study designs.

4. Conclusions

Over the last few decades, HPA axis activity and reactivity has been studied extensively and evidence has been collected for its importance in health and disease. Two disorders that received considerable attention are depression and PTSD. In this context, our knowledge and understanding of how changes in the signaling cascade, both intracellularly and with regard to feedback sensitivity of the axis, are linked to disease outcomes has been increased significantly. However, to advance this line of research, an important next step has to be to assess not only the different components of the axis itself, but to enrich current disease models focusing on the HPA axis by incorporating the effects of glucocorticoids on other systems (and the effects of those systems on the HPA axis).

In the current review, we presented data from studies investigating the GC sensitivity of two effector systems implicated in depression and PTSD, the immune system, specifically inflammatory processes, and the CNS. The evidence summarized on the previous pages thereby points to opposite patterns of glucocorticoid sensitivity alterations within these systems in PTSD and depression. While central nervous system sensitivity to glucocorticoids is increased in PTSD, as indicated by higher GC inhibition of memory, the opposite is true for depression. Furthermore, peripheral immune function, although similarly over-active with regard to the inflammatory cascade, displays a higher sensitivity to GC control in PTSD and a lower sensitivity in depression. This taken together with the typical findings on HPA axis functioning in these two psychiatric disorders, we come to the same conclusion as Raison and Miller (2003): although GC sensitivity of the two target tissues reviewed here is altered in opposite directions, the results can be summarized as an inefficient GC signaling in both disorders, depression and PTSD. A summary of these data is provided in Fig. 5.

However, as pointed out previously, so far only little data exist on GC sensitivity of effector systems. Consequently, many questions remain unanswered, some of which will be discussed in the following.

Central and peripheral GC sensitivity appears to be altered in a similar fashion within each disorder, i.e. both are increased in PTSD and decreased in depression. But are central and peripheral GC sensitivity statistically associated? For example, could an in vitro immunoassay be used as a test for central GC sensitivity? Theoretically, the GC signaling cascade can be subjected to different modulating factors in different tissues, such as inflammatory cytokine concentrations that induce GC resistance (e.g. Pace et al., 2007) might differ between peripheral blood and CNS structures, and expression of GRs and MRs has also been shown to vary between peripheral tissues (Miller et al., 1990). Nevertheless, some factors, such as polymorphisms are also constant within individuals. However, since the same polymorphism can have different effects, for example, in different brain areas, it is not surprising that earlier studies on healthy participants were usually less successful in finding associations between different tissues' GC sensitivity (e.g. Ebrecht et al., 2000). It should be pointed out that cognitive GC sensitivity as presented in this paper was also not measured in those earlier studies. However, we were able to show associations of GC sensitivity of emotional memory with sensitivity of peripheral inflammation in a recent study (Rohleder et al.,

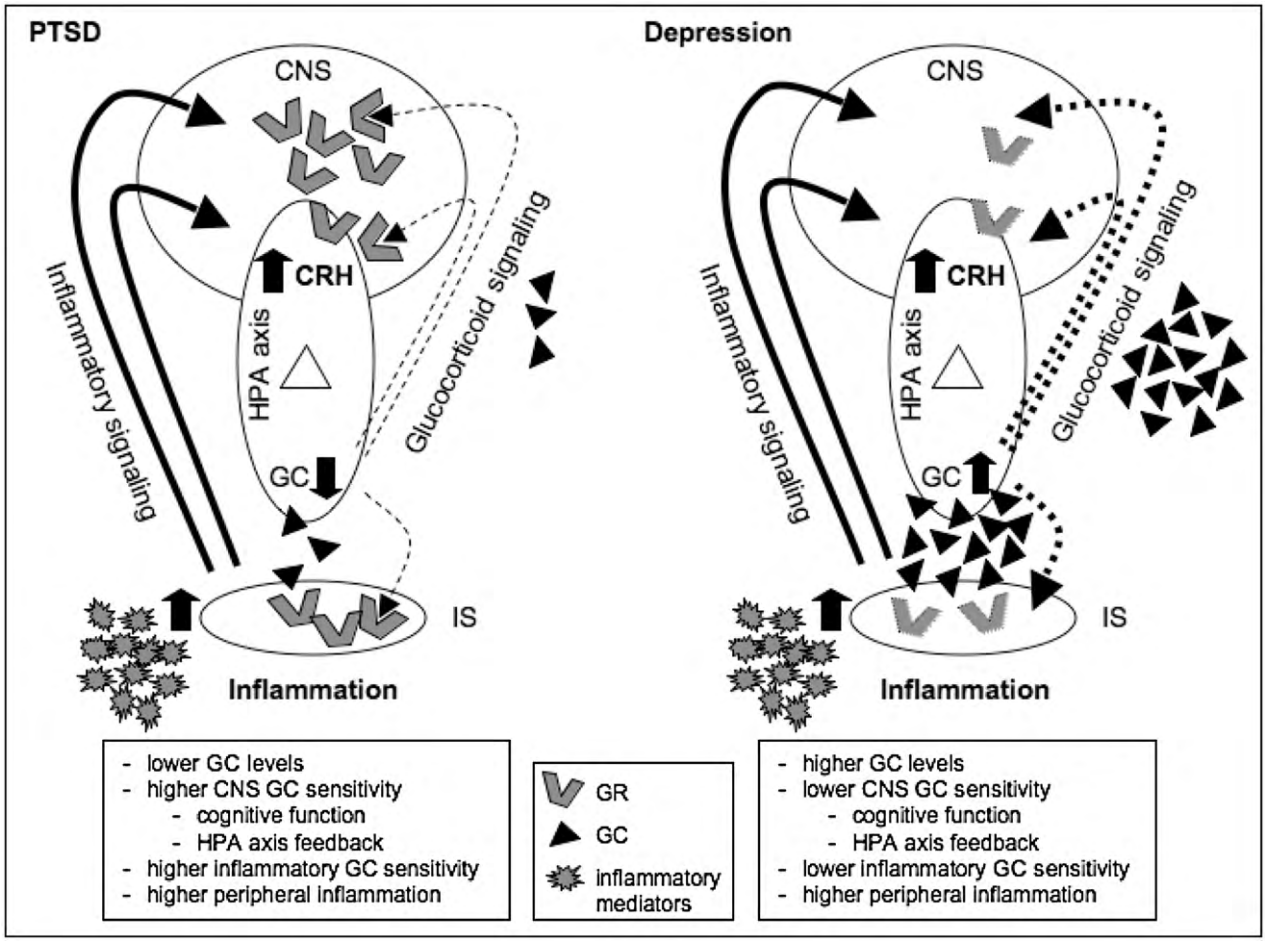

Fig. 5. This figure summarizes current data on cognitive and inflammatory glucocorticoid sensitivity in depression and posttraumatic stress disorder. Bold arrows represent inflammatory signaling into the CNS, while dotted arrows represent glucocorticoid (GC) signaling into the CNS and to inflammatory tissues. Ability to receive GC signals (GC sensitivity) is symbolized by more and bold GRs in PTSD, and by fewer GRs with dotted borders in depression. A contribution of MR alterations in MDD and PTSD has been suggested more recently, but remains to be established. MR findings are thus not incorporated into the current working model.

2009b). How this will translate to other memory and immune functions will be an interesting question for future research.

A further set of questions raised by the summary of findings in Fig. 5 relates to our understanding of the specific alterations in GC signaling in depression and PTSD. While it seems to be clear that inflammatory disinhibition is a characteristic of both disorders, it is unclear whether inflammatory disinhibition is a consequence of altered GC signaling or a cause for altered HPA axis activity and reactivity. The same is true with regard to changes in cognitive functions. Based on current data, several models are conceivable:

For example, inflammatory disinhibition including increased inflammatory signaling to the CNS might induce changes in cognitive GC sensitivity, which might affect memory as shown in PTSD, or mood as shown in depression and PTSD (e.g. Dantzer et al., 2008; Raison et al., 2006). Furthermore, inflammatory signaling is expected to decrease GC sensitivity (Pace et al., 2007), and thus might also be responsible for increased HPA axis activity (e.g. Maes et al., 1993). However, while this pathway fits findings in depression, it cannot explain the increased HPA axis feedback sensitivity typically observed in PTSD.

Another potential pathway could start in the CNS, where alterations in central GC sensitivity might lead to changes in HPA axis functioning, including altered peripheral cortisol concentrations. These alterations could via ligand-dependent regulation induce alterations in peripheral GC sensitivity. In the case of PTSD, higher HPA axis feedback sensitivity could explain lower peripheral cortisol, which in turn would be responsible for the increased peripheral GC sensitivity and importantly, inflammatory disinhibition observed in this disease. In the case of depression, however, lower central GC sensitivity might explain HPA axis overactivity with higher circulating cortisol concentrations, which might lead to compensatory down-regulation of peripheral GC sensitivity, and thus permit inflammatory disinhibition. The latter model suggests that in the case of PTSD, lower cortisol concentrations or missing counter-regulation via alteration in peripheral GC sensitivity is the problem, while in depression, compensatory mechanisms resulting in a down-regulated peripheral GC sensitivity would be the cause for increased inflammatory activity. This raises the question whether altered GC sensitivity is a simple consequence of the respective disorder, or whether altered GC sensitivity is a vulnerability factor or predisposing condition for depression or PTSD.

With regard to PTSD, Pitman et al. (2006) have addressed the question of acquired versus pre-existing alterations in a study of twin pairs discordant for combat exposure, and found that hippocampus volume, although lower in PTSD, was not determined by combat exposure, but was a pre-existing condition (Pitman et al., 2006). HPA axis activity or GC sensitivity of any of the systems discussed here was not reported, but given the importance of the hippocampus in cognitive function (Wolf, 2008) and HPA axis feedback, this finding might be indicative of pre-existing alterations in central GC sensitivity in PTSD. With regard

to depression, Heim et al. (2008) have summarized data on the effects of early life experience on HPA axis function and development of depression, and come to the conclusion that many changes induced by childhood maltreatment, including altered HPA axis feedback sensitivity, resemble those found in depression, and might thus be seen as a pre-existing vulnerability factor (Heim et al., 2008). Similar results have recently been reported for inflammation. Danese et al. (2008) showed that childhood maltreatment was associated with both, inflammation and depression, in later life (Danese et al., 2008). Lastly, findings such as summarized for GR and FKBP5 polymorphisms also suggest that specific predisposing conditions might exists. However, they also show that those predisposing conditions might not necessarily always induce the same counter-regulatory processes in all contexts. Unfortunately, so far, no study assessed all the different sensitivity measures at the same time and importantly, also repeatedly over time and thus it is difficult to decide whether the findings represent features independent from influences by other systems or whether they are the result of compensatory processes, including those driven by (other) effector systems. Elucidating the timely resolution of the interplay between the various systems' GC sensitivity will be an important task for future studies.

Furthermore, we presented data on moderators of GC signaling and thus GC sensitivity that were also implicated in depression and PTSD (e.g., GR and FKBP5 polymorphisms). Generally, given the multitude of those moderators, we argued that the assessment of GC sensitivity of a target tissue represents a way to measure the combined effect of all those potential changes in moderators and thus is advantageous over the assessment of single parameters. However, it will be a future task to relate intra-individual changes and inter-individual differences in each of those moderators not only to GC feedback sensitivity, but also to GC sensitivities of other tissues, thus helping to explain the mechanisms underlying an altered interplay between various tissues' GC sensitivities. In this context the investigation of the differential role of the two receptors (MR and GR) appears to be an important target for future research, especially for the enhanced understanding of central/cognitive GC sensitivity (Joels et al., 2008). A limitation of the model is the comorbidity between MDD and PTSD (e.g. Campbell et al., 2007). Since most of the data supporting our model comes from patients without substantial comorbidity, the model in its current version only applies to GC sensitivity observed in 'pure' forms of the disorders. Future studies are needed in order to tests whether comorbidity of both disorders is associated with enhanced, impaired or unaltered GC sensitivity. Past studies on this topic have lead to rather inconclusive results (e.g. Vythilingam et al., 2009; Yehuda et al., 2004; de Kloet et al., 2008) most likely reflecting the large inter- and intra-individual variance within each patient population.

Taken together, there is accumulating evidence for the fact that besides alteration in the HPA axis itself, alterations in central and peripheral glucocorticoid sensitivity play an important role in depression and PTSD. Unfortunately, so far data on both, inflammatory and cognitive GC sensitivity, are scarce and therefore still somewhat preliminary. However, because of the important role of memory and other cognitive functions in the development of stress-related psychiatric disorders and the important health implications of alterations in the tight interplay between endocrine and immune system, we argue that it is central for our understanding of disease development and progression to increase our data on inflammatory and cognitive GC sensitivity in psychiatric disorders. Only a disease model that incorporates all systems affected by depression and PTSD will allow for successful treatment development, including the assessment of glucocorticoid's potential in pharmacological treatment (as discussed for PTSD, e.g. Yehuda and Golier, 2009). Assessment of GC sensitivity of various target tissues thereby represents an easy, yet comprehensive method that will advance our knowledge beyond what we can learn from exploring HPA axis feedback sensitivity and genetic and epigenetic effects on GC signaling pathway in the context of depression and PTSD.

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