KEY POINTS

- Corticosteroids function to optimize the stress response and are thus essential for the organism to cope with the stressor.
- Corticosteroid signaling is mediated by two receptors: the high-affinity mineralocorticoid receptor and the low-affinity glucocorticoid receptor.
- Imbalance between central glucocorticoid and mineralocorticoid receptor affects the secretion of corticosteroids and has profound consequences for adaptation to stress.
- Single nucleotide polymorphisms in the glucocorticoid receptor gene affect not only corticosteroid production and secretion but also the effects of corticosteroids in different physiological and behavioral systems.
- Other influences such as trauma can permanently alter the glucocorticoid/mineralocorticoid receptor balance.

1. INTRODUCTION

1.1. Stress and Homeostasis

When deviations in physiological or behavioral parameters exceed a certain threshold, central release of corticotropin-releasing hormone (CRH) from the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) is triggered. CRH activates, in the specific context of the stressor, the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, which promote a series of physiological and behavioral adaptations in order to reestablish homeostasis (McEwen, 1998). Multiple afferents can activate CRH neurons, each conveying specific stressful information. These afferents can be ascending direct innervations from the brainstem that relay stressors of systemic origin (metabolic demands, fluid loss, pain, inflammation). Sensory cognitive and emotional information also reaches via a complex transsynaptic pathway—the PVN (Herman et al., 2003). The summation of all inputs to the PVN provides an output that can be measured as the threshold for activation of these neurons as well as the rate of onset, magnitude and duration of the response. The type of afferent input additionally determines the composition of the cocktail of adrenocorticotropic hormone (ACTH) secretagogues released with CRH in interaction with other stress hormones (e.g., norepinephrine [NE] and epinephrine [E]) (Goldstein, 2003; Herman et al., 2003; Romero &
Sapolsky, 1996). This initial CRH-mediated stress reaction is counterbalanced by the stress-induced elevation in circulating levels of glucocorticoids and by parasympathetic nervous system activity. Recently it has been suggested that the CRH-2 receptor system is prominent in the coordination of these later slow responses, facilitating the recovery of homeostasis (Hsu & Hsueh, 2001; Reul & Holsboer, 2002).

1.2. HPA Axis Regulation

Corticosteroids are secreted from the adrenal gland under the control of ACTH of pituitary origin. In turn, ACTH is mainly under the regulatory influence of hypothalamic CRH. In addition, the hippocampus, a limbic brain structure involved in behavioral adaptation, exerts a tonic inhibitory control over these secretagogues. Furthermore, a strong negative feedback effect influences the secretion of ACTH and CRH exerted by cortisol at the level of the pituitary and PVN respectively. Three features with respect to the regulation of the HPA axis need further attention.

First, depending on the nature of the stressor, it seems that different cocktails of ACTH secretagogues, with respect to absolute and relative concentrations, are released from the PVN. ACTH then enters the circulation and induces the production and secretion of corticosteroids from the adrenal glands—predominantly cortisol in humans and corticosterone in rodents. Both physical and psychosocial stimuli—real, anticipated, or imagined—that modulate emotional and cognitive processes can be stressors. This processing of psychosocial information occurs in the so-called limbic structures, including the amygdala, hippocampus, and frontal cortex, which modulate CRH release transsynaptically via a $\gamma$-aminobutyric acid (GABA)-ergic network surrounding the PVN (Herman, Cullinan, Ziegler, & Tasker, 2002). Collectively, the PVN integrates the inhibitory and excitatory signals producing its cocktail of ACTH secretagogues (Windle, Wood, Shanks, Lightman, & Ingram, 1998; Goldstein, 2003).

A second important feature of the HPA axis is the existence of an ultradian rhythm of about one pulse per hour resulting in phasic release of hormones (Lightman et al., 2000). It is unlikely that levels of CBG are changing rapidly enough to counteract the dynamic fluctuation in total plasma corticosteroids, suggesting the same large fluctuations for free plasma corticosteroids (Windle et al., 1998). The pulse generator seems localized in the hypothalamus, but its identity is largely unknown. However, at the level of the adrenals important modulations occur through a transsynaptic descending pathway from the suprachiasmatic pacemaker (Kalsbeek & Buijs, 2002). This nervous input changes adrenal sensitivity to ACTH in a circadian fashion. Altered ultradian rhythms are observed, and recent studies suggest that previous early experiences as well as the nature of the stressor are important determinants for HPA axis pulsatility. It is thought that the pattern (e.g., fast short-lasting vs slow long-lasting increase) rather than the absolute amount of circulating stress hormone is the important determinant in adaptive or maladaptive effects of HPA axis activation.

Third, corticosteroids target those stress centers in the brain involved in adaptive responses and regulation of the HPA axis. These actions exerted by corticosteroids proceed in different time domains. The rapid nongenomic corticosteroid action modulating the HPA axis pulse and associated behaviors is still poorly understood. It may involve at the membrane rapid assembly of molecular aggregates or second messenger signaling cascades. The genomic actions of corticosteroids are much better documented. These
actions are mediated by high-affinity mineralocorticoid receptors (MRs) and lower-affinity glucocorticoid receptors (GRs), which are co-localized in abundance, particularly in limbic neurons, such as the hippocampus. Because of the stress-induced signaling cascades that occur in the various afferents to the PVN, the actions of corticosteroids mediated by these two different types of receptors present with enormous diversity. We postulated that the balance in MR- and GR-mediated actions is essential for homeostasis, adaptation, and resilience (de Kloet, 1991; de Kloet, Vreugdenhil, Oitzl, & Joëls, 1998). Via MR-mediated actions, corticosteroids set signaling pathways at a certain threshold, which determines how and how fast the response to stress occurs. This helps in the appraisal of the nature and the severity of the stressor and facilitates the retrieval of an appropriate physiological response and/or behavioral coping style. GRs promote recovery and adaptation while facilitating the behavioral response in order to be prepared at the next encounter.

A large part of our knowledge leading to the MR/GR balance concept has been obtained by selective blockade of one or the other receptor type following intracerebral application of antagonists, which have been tested using different behavioral paradigms (Oitzl & de Kloet, 1992; Oitzl, Fluttert, & de Kloet, 1994). In addition, mouse mutants in which the GR or MR have been knocked out (Oitzl, Reichard, Joëls, & de Kloet, 2001; Reichard et al., 1998) or downregulated have been used (Montkowski et al., 1995). In testing stress system regulation, investigators are faced with the problem that the significance of MR- and GR-mediated actions in the various brain circuits and afferent inputs to the PVN is still largely unknown. Therefore, it is important to identify the search for factors that may change the MR/GR balance (see Fig. 1). Defining these signaling pathways will help to determine the predisposition and pathogenesis of stress-related disorders.

2. MR/GR BALANCE

2.1. Intracellular Level

Since the MR in the brain has a very high affinity for corticosterone (and aldosterone), the 1-h pulses of corticosterone in the ultradian adrenal rhythm are predicted to maintain a stable, near-saturation, occupancy of the MR in brain (de Kloet, 1975). In contrast, the GR has too low an affinity to become activated by low nonstress concentrations of corticosterone in vivo. Only following stress levels of corticosteroids does activation occur, and receptor translocation to the nucleus varies in parallel with the circulating corticosterone levels (Kitchener, Di Blasi, Borelli, & Piazza, 2004). These receptor studies are performed mainly with hippocampal tissue in which MR and GR are co-localized (van Steensel et al., 1996). The MR seems to be predominantly located in the nuclear compartment, even under basal resting pulsatile conditions, whereas GR only translocates during the peaks of corticosterone pulses (van Steensel et al., 1996). As a result of the differential corticosteroid receptor locations, different patterns of corticosteroid genes are affected. Using a paradigm of (a) absence of, (b) low, and (c) high corticosterone, we discriminated MR-responsive, MR + GR-responsive, and GR-responsive genes in the rat hippocampus (Fig. 2) (Datson, van der Perk, de Kloet, & Vreugdenhil, 2001). This indicates that, depending on relative MR and GR activity, distinct patterns of gene activity are induced.
Fig. 1. Factors involved in central corticosteroid-signaling—the MR/GR balance. CRH is the main driving hypothalamic secretagogue inducing ACTH secretion from the pituitary gland. In turn, ACTH induces increased production and secretion of cortisol from the adrenals. In the circulation, cortisol is bound to cortisol-binding globulin (CBG), limiting the concentration of free cortisol (the active fraction) and clearance by the liver. In case of central effects, cortisol access is further limited by the Pgp located at the BBB, which excludes cortisol to a certain extent from the brain. Additional regulation is accomplished by two 11β-HSD isoenzymes: 11β-HSD-I regenerates cortisol from (inactive) cortisone, while 11β-HSD-II does the opposite. Cortisol binds with high affinity to the MR and with approx 10× lower affinity to the GR. Genomic activity is modified by direct DNA binding or by interaction with other transcription factors such as AP-1 or NF-κB. Direct DNA binding is influenced by SRCs and the composition of the target promoter region. These factors influence the MR/GR balance and their effects on, for example, target gene expression (see Fig. 2). In addition, genetic variability can influence protein expression and amino acid sequence. Changes in amino acid sequence could hypothetically induce changes in phosphorylation capacity, higher affinity, or diminished dimerization. As a result, corticosteroid effects will shift towards a certain effect/direction (e.g., NF-κB interaction) and away from another (e.g., direct DNA binding), leading to a condition with a less favourable metabolic profile, more HPA axis reactivity, high blood pressure, or being inflammatory-prone. Abbreviations: ACTH, adrenocorticotropic hormone; AP-1, activation protein-1; BBB, blood–brain barrier; CRH, corticotropin-releasing hormone; 11βHSD-I, 11β-hydroxysteroid dehydrogenase, active as a reductase; CBG, cortisol-binding globulin; HPA, hypothalamic–pituitary–adrenal; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; NF-κB, nuclear factor κB; Pgp, P glycoprotein; SRCs, steroid receptor coactivators.

2.2. Cellular Level

Using the CA1 pyramidal neurons in the hippocampal slice as a model, two general principles were revealed (Joëls & de Kloet, 1989, 1992, 1994). First, the control exerted by MR and/or GR appeared to proceed in a U-shaped manner. Maximal ion conductance
and transmitter responses were seen in the absence of corticosterone when no receptor was active. The same pattern was observed in the presence of very high supraphysiological concentrations of the steroid when both receptors were active. Intermediate corticosterone concentrations occupying predominantly MR and little GR minimize the cell responses. These concentrations are thought to represent the average steroid concentration during the day. Second, these responses form the mechanistic basis for phenomena on the network level such as long-term potentiation (LTP), which also have been demonstrated to show a U-shaped dose-responsiveness to corticosterone (Diamond, Bennett, Fleshner, & Rose, 1992). Thus, at least in hippocampal neurons, cellular work demonstrates that MR stabilizes excitability on the cell and circuit level in the hippocampus, and GR modulates excitability transiently raised by stimulatory stimuli.

Fig 2. MR- and GR-responsive genes in the rat hippocampus. Following adrenalectomy (ADX), rats were supplied with low (LC) or high levels (HC) of corticosterone. The transition from depleted to low corticosterone levels will involve MR activity because no GRs will be occupied. Ninety-eight genes were identified to be exclusively MR-responsive, being induced (F; 49) or downregulated (E; 49). Seventy-two genes were found to be exclusively GR-responsive—36 upregulated (G; 36) and 36 downregulated (H; 36). Interestingly, 33 genes were both MR- and GR-responsive, showing down- and upregulation (A–D). Changes in MR or GR expression, intrinsic activity (owing to gene polymorphism), corticosteroid availability, cofactors, and other transcription factors will direct the pool of corticosteroid-responsive genes in a certain direction: e.g., predominant MR activity in combination with low GR activity will skew gene regulation to the 98 and 33 pools, away from the 72 pool. One result will be that the exclusively GR-responsive genes will lack control by high stress levels of corticosteroids, possibly leading to an overreactive stress response, with all the accompanying dangers. (Reprinted with permission from Datson et al., 2001.)
The aforementioned MR- and GR-mediated changes in excitability in the hippocampus have consequences for the excitatory output of the system. Changes in MR-regulated thresholds can increase or decrease responsiveness of neurons critical for the regulation of the PVN. It is thought that MR maintains a high excitatory tone mediated by glutamate, which can be attenuated by transient GR activation. The excitatory outflow is thought to activate the GABA-ergic network around the PVN. A few studies have shown that the GABA-ergic input to the PVN changes as a function of corticosteroid exposure both in characteristics and the number of synaptic contacts (Joëls, Verkuyl, & van Riel, 2003).

2.3. Behavioral Level

On the behavioral level, the brain site and circuit activated, the context of the stressor, and the activity of the central corticosteroid receptors determine the final outcome. Thus, if MR is blocked in the medial amygdala or the circumventricular organs, one typically interferes with mineralocorticoid control of salt appetite (Sakai, Ma, Zhang, McEwen, & Fluharty, 1996), because these sites contain aldosterone-selective MR. However, if MR is blocked elsewhere, a plethora of effects has been observed that can be summarized as follows.

MR blockade attenuates autonomic outflow (Rahmouni, Barthelmbs, Grima, Imbs, & de Jong, 2003; van den Berg, de Kloet, & de Jong, 1994; van den Buuse, van Acker, Fluttert, & de Kloet, 2002) in regulation of cardiovascular and renal function. MR antagonists block the conservation/withdrawal response if animals are exposed to a severe stressor (Korte, 2002) and disrupts conditioning processes as observed in the forced extinction of an inhibitory avoidance response (Bohus & de Kloet, 1981). These responses suggest rapid anxiolytic effects of centrally administered MR antagonists, which proceed independently from direct interaction with the GABA-A receptor. Also, with a time delay of only a few minutes MR activation enhances aggressive behavior of a resident mouse towards an intruder (Haller, Millar, & Kruk, 1998). In spatial learning tests MR rapidly affects interpretation of environmental information and selection of the appropriate behavioral response to deal with the challenge. Experimental evidence for this thesis comes from the findings that administration of a few nanograms of mineralocorticoid antagonist icv immediately before testing altered the behavioral pattern of an animal in a maze to find food that it had learned to locate the previous day or to search for an escape route (Oitzl et al., 1994). How these mostly rapid MR-mediated effects occur is not known.

Blockade of brain GR impairs the storage of new information (Loscertales, Rose, & Sandi, 1997; Oitzl & de Kloet, 1992). A glucocorticoid antagonist administered around the time of learning in the hippocampus or in the amygdala impaired the consolidation of newly acquired information (Roozendaal, Griffith, Buranday, Quervain, & McGaugh, 2003). As a consequence 24 h later the rat is unable to retrieve the information learned the previous day and has to learn the maze problem all over again. Likewise, mutant mice with a point mutation in GR that obliterates binding to DNA are unable to store learned information (Oitzl et al., 2001). This suggests that corticosteroid-induced cognitive performance requires transactivation, as was previously found in the cellular responses to corticosterone in hippocampus (Karst et al., 2000), because such mutants lack the direct activation of GRs, but still have a GR that can interact with other transcription factors (Reichardt, Tuckermann, Bauer, & Schütz, 2000). Transgenic mice with downregulated
GRs (knockdown) show cognitive defects and elevated plasma ACTH and corticosterone concentrations in response to stress (Müller, Holsboer, & Kellendonk, 2002).

The above studies are based mostly on observations in rodents, but observations in humans largely agree (Buchanan & Lovallo, 2001; Lupien et al., 2002; Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999; Wolkowitz et al., 1990). In general, the data show that MR plays a role in the interpretation of environmental stimuli and affects the animal’s reactivity and behavioral response pattern. These effects are mostly rapid, but the underlying (nongenomic) mechanism is not known. Much confusion has been created in the literature about the role of GR. Blockade of the GR clearly demonstrates its facilitatory role in the storage of new information. However, if the receptor is stimulated beyond the context of the learning experience (e.g., at retrieval) the learned response is considered no longer relevant, and the animal switches to a more opportune response. Mice exposed to chronic stress and high corticosterone concentrations deteriorate in spatial learning, whereas the reverse occurs after chronic treatment with GR antagonists. Chronic GR blockade in brain appears to result in enhancement of cognitive performance (Oitzl, Fluttert, Sutanto, & de Kloet, 1998).

2.4. Neuroendocrine Control

Intracerebral blockade of MRs and GRs using selective antagonists exerts a profound and differential effect on HPA axis activity. We also distinguished the blockade of GRs in the HPA core (i.e., pituitary corticotrophs and PVN microenvironment) from the blockade of MRs and/or GRs in stressor-specific afferents from prefrontal cortex, hippocampus, brainstem, amygdala-locus coeruleus, and other forebrain structures. The latter blockade interferes with processing of information and behavioral responses and leads to subsequent changes in HPA regulation. Thus, exposure to a novel environment was used as a stressor, since the limbic-cortical brain circuits involved in responding to a novel situation (e.g., fear, attention, appraisal, and reward) abundantly express MRs and GRs.

In adrenal intact animals, the results showed that application of the MR antagonist RU 28318 icv causes a rise in basal trough and peak levels of HPA activity during basal nonstress conditions as well as an enhanced response to the novelty stressor (Ratka, Sutanto, Bloemers, & de Kloet, 1989). In humans MR blockade enhances HPA activity (Deuschle et al., 1998; Dodt, Kern, Fehm, & Born, 1993; Heuser, Deuschle, Weber, Stalla, & Holsboer, 2000; Young, Lopez, Murphy-Weinberg, Watson, & Akil, 1998). As expected, the GR antagonist mifepristone had no effect on basal trough activity because no GR is occupied under these conditions. Rather a prolonged response to the novelty stressor was observed after GR blockade (Ratka et al., 1989). The attenuation of the novelty-induced response was mimicked with antagonist application in the dorsal hippocampus, whereas the prolonged response required GR blockade in the PVN (de Kloet, de Kock, Schild, & Veldhuis, 1988; Oitzl, van Haarst, Sutanto, & de Kloet, 1995; van Haarst, Oitzl, & de Kloet, 1997). After continuous infusion of a few nanograms of mifepristone icv the amplitude of the circadian rhythm became greatly enhanced after 4 d because the peak rather than the trough levels in HPA axis activity increased (van Haarst, Oitzl, Workel, & de Kloet, 1996). As is the case in the rat, chronic mifepristone enhanced the amplitude of the flattened circadian rhythm in cortisol characteristic of the disease (Belanoff et al., 2002).
3. ACCESS TO CORTICOSTEROID RECEPTORS

3.1. Corticosteroid-Binding Globulin

Only a small proportion of circulating corticosteroids is free, which is the active fraction. Several proteins in the circulation are capable of binding corticosteroids, but, corticosteroid-binding globulin (CBG) is the most important. CBG circulates during young and adult life, but is virtually absent from the circulation during the first 2 wk of life. This may account for the very strong postnatal glucocorticoid feedback signal observed. CBG-bound steroid is thought to be bio-inactive, and according to this view CBG serves as a pool from which glucocorticoids are made available. CBG is expressed in liver but also at low levels in a range of glucocorticoid target tissues. Besides its “buffer” function, CBG is a member of the serine protease inhibitors and is a substrate for neutrophil elastase (SERPINS). There is evidence suggesting a specific interaction between CBG and elastase on the surface of neutrophils, which may promote the delivery of glucocorticoids at sites of inflammation or perhaps other tissues affected by stress (Hammond, Smith, Paterson, & Sibbald, 1990). The role of CBG in the delivery of glucocorticoids to the brain is not known, although high levels have been found in the pituitary gland.

3.2. 11β-Hydroxy-Oxido-Reductase

Two isoenzymes exist for 11β-steroid dehydrogenase (Seckl & Walker, 2001). 11β-Steroid dehydrogenase type 2 is an NAD(H)-dependent enzyme that functions as an oxidase and is found co-localized with MR in tissues that selectively respond to the mineralocorticoid aldosterone. Aldosterone circulates at approx 1000 times lower concentrations as compared to corticosteroids, which makes it necessary to “protect” these tissues from high levels of corticosterone/cortisol. Type 2 is localized in kidney and in brain circumventricular organs, where it conveys aldosterone selectivity because of local intracellular metabolic conversion of the naturally occurring glucocorticoids cortisol and corticosterone (Edwards et al., 1988; Seckl & Walker, 2001). 11β-steroid dehydrogenase type 1 is an NADP(H)-dependent enzyme that functions mainly as a reductase in the cell to generate active cortisol and corticosterone from inactive 11-dehydrocorticosterone. The type-1 enzyme is widely distributed. The enzyme is also located in brain, where it may regenerate bioactive corticosteroids.

3.3. Multidrug-Resistance P-Glycoprotein

Dexamethasone in low concentrations penetrates the brain poorly, but is accumulated in pituitary corticotrophs (de Kloet, 1975; Meijer et al., 1998). We have shown that the synthetic steroid is extruded by multidrug-resistance P-glycoprotein (mdr Pgp) and related proteins in the blood–brain barrier. These Pgps play a role in mdr, such as with cancer. Using Pgp knockout mice a 10-fold higher accumulation of 3H-dexamethasone was observed in the brain of the mutants. 3H-cortisol, not naturally occurring in rat and mouse, is also poorly retained in wild type rodent brains and appears as a Pgp substrate. In the Pgp mutants profound labeling of hippocampal neurons occurs with cortisol, as is the case with corticosterone. To our surprise, human mdr also recognizes cortisol rather than corticosterone as substrate, and liquid chromatography–mass spectrometry analysis of postmortem human brain samples revealed that corticosterone is preferred by the
human brain more often than cortisol (Karssen et al., 2001). In plasma the ratio of cortisol to corticosterone is approx 20, whereas in brain it was often 3.3. Thus, it is possible that human mdr differs in specificity for cortisol and corticosterone.

3.4. Transcription Factors and Coregulators

On binding ligand, MRs and GRs can both bind to glucocorticoid response elements (GREs, consensus sites located on the DNA), but only GRs can interact with transcription factors (proteins) such as activating protein (AP-1) and nuclear factor-κB (NF-κB) (Auphan, DiDonato, Rosette, Helmberg, & Karin, 1995; De Bosscher, Vanden Berghe, & Haegeman, 2003). It is now known that they achieve this blockade through interaction of the GR monomers with transcription factors activated by signaling cascades driven by several stress factors. This finding provides a firm mechanistic underpinning to the concept advanced by Tausk (1951) and Munck, Guyre, and Holbrook (1984) that a major action of glucocorticoids is to block primary stress reactions.

Recently, coregulator molecules were identified that appeared to be powerful modulators of nuclear receptor function (Meijer, Steenbergen, & de Kloet, 2002). Members of the steroid receptor coactivator (SRC) family of proteins promote agonist-induced receptor activation by permitting recruitment of, for example, CBP/p300 transcription activators. The corepressor molecules do the opposite and promote repression of gene transcription. The GR antagonist mifepristone (RU 486) with the receptors provides an interesting example of the possible modes of interaction with steroid receptor signaling. This antagonist only acts as an antagonist (at GREs) if sufficient corepressor is available. In vitro transfection experiments suggest that variable stoechiometry of corepressors and co-activators may underlie differential MR/GR functioning.

4. VARIANTS OF THE GLUCOCORTICOID RECEPTOR

In 1985 two different human (h)GR cDNAs were cloned: hGRα and hGRβ cDNA, which were later shown to encode the α and β isoforms of the receptor (Hollenberg et al., 1985) (Fig. 3). hGRα and hGRβ mRNA both contain exons 1–8 but have different versions of exon 9 as a result of alternative splicing; hGRα mRNA contains exon 9α, whereas hGRβ mRNA contains exon 9β (Oakley, Sar, & Cidlowski, 1996). In addition, hGR mRNA may contain five different versions of exon 1. Through the usage of the three different promoters, three different exons 1 can be transcribed (1A, 1B, and 1C), and alternative splicing of exon 1A can result in yet three different versions (1A1, 1A2, 1A3) (Breslin, Geng, & Vedeckis, 2001). Like other members of the steroid receptor family, the hGR contains three major domains (Giguere, Hollenberg, Rosenfeld, & Evans, 2001; Weinberger, Hollenberg, Rosenfeld, & Evans, 1985). The most N-terminal domain is called the immunogenic domain, which in hGR consists of amino acids (AAs) 1–420. AAs 421–488 form the DNA-binding domain (DBD) of hGRα, and its C-terminal ligand-binding domain (LBD) consists of AAs 527–777, of which the last 50 AAs are encoded by exon 9α. The LBD of hGRβ is similar to that of hGRα until AA 727, at which point the last 15 AA are encoded by exon 9β. After that hGRα and hGRβ diverge, and 15 unique AAs form the most C-terminal part of hGRβ LBD.

Recently it has been shown that alternative translation initiation results in the presence of two different isoforms (A and B) of hGRα (Yudt & Cidlowski, 2001). An alternative start site for translation is formed at codon 27, encoding methionine. This results in a
Fig. 3. Factors involved in corticosteroid signaling. Cortisol is released from the adrenal glands binds to cortisol-binding globulin (CBG) in the circulation, thereby protecting the hormone against degradation by liver P450 enzymes. In the target tissue, cortisol can be converted to the inert cortisone by 11β-HSD-II or reactivated by 11β-HSD-I. At the GR level, the amount, degree of phosphorylation, and affinity (the latter being influenced by binding of the unliganded GR to several heat shock proteins) directly determine corticosteroid responsiveness. Several variants of the GR exist, of which GRβ is thought to function as a natural inhibitor of the classical GR, GRα (Bamberger, Bamberger, de Castro, & Chrousos, 1995; DeRijk, Sternberg, & de Kloet, 1997). In addition, two translationary variants exist, GR-A and GR-B, using two different translation start sites, both at the beginning of exon 2 (Yudt & Cidlowski, 2001). GR-B seems to be even more active as compared to the classic GR(α)-A. At the DNA level, a “simple” glucocorticoid-responsive element (GRE) can exert a positive or negative action on gene transcription after direct binding of GR homodimers. This mode of action seems to be most important in metabolic actions, such as activation of the enzyme phosphoenol pyruvate carboxykinase (PEP-CK). In contrast to direct binding to DNA, GR can interact with other transcription factors such as AP-1, NF-κB, or cAMP-responsive element-binding protein (CREB), often resulting in mutual inhibition (De Bosscher et al., 2003). These activities are important in immune function, cardiovascular control, growth and development, and behavior. Finally, chromatin structure or modulation of chromatin structure, e.g., by histones, determines access of the receptors to nuclear-binding sites.

Mutations within the GR gene are not compatible with life or result in severe corticosteroid-resistance syndrome. This is owing to their pleiotropic actions (see Figs. 1 and 3), and their effects on almost every physiological and behavioral system. The corticosteroid-resistance syndrome is characterized by hypertension, excess androgens, and increased plasma cortisol concentration in the absence of the stigmata of Cushing’s syndrome (Brönnegård & Carlstedt-Duke, 1995; Charmandari et al., 2004; Chrousos, Detera-Wadleigh, & Karl, 1993; Lamberts, Huizenga, de Lange, de Jong, & Koper, 1993). A similar mechanism of alternative translation initiation has been proposed for hGRβ, but this has not yet been demonstrated.
Moreover, several GR-gene mutations have been found in human malignancies, including Cushing’s disease (for review, see DeRijk, Schaaf, & de Kloet, 2002). In addition, naturally occurring GR-gene polymorphisms have been found that are not directly associated with overt disease (Lamberts et al., 1996) (Fig. 4; Table 1). However, some GR-gene single-nucleotide polymorphisms (SNPs) have been associated with diseases such as obesity, cardiovascular diseases, and autoimmunity (Table 1). Three GR-gene polymorphisms have received much attention: ER22/23EK, located at the beginning of exon 2; N363S, located at the end of exon 2; Bcl1 site downstream of exon 2, being an allele spanning almost the entire intron B (±80 kB) and the A to G in exon 9β in the ATTTA site. For the effects of these SNPs, see text.

Fig. 4. Single-nucleotide polymorphisms (SNPs) in the GR gene. Schematic overview of the GR gene. Translation starts at the beginning of exon 2 and ends in exon 9. Several splice variants exist: different exon 1s have been described (Breslin et al., 2001), whereas exon 8 can join exon 9α or 9β, giving rise to GRα or GRβ, respectively. Recently, Yudt and Cidlowski (2001) described a GR-translation variant, designated GR-B, with a potential high effect on gene expression. Depicted are Thh111 located between exon 1c and 1b, ER22/23EK at the beginning of exon 2, N363S at the end of exon 2, Bcl1 site downstream of exon 2, being an allele spanning almost the entire intron B (±80 kB) and the A to G in exon 9β in the ATTTA site. For the effects of these SNPs, see text.

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4.1. Cardiovascular Control

Glucocorticoids have long been associated with increased vascular tone and cardiac output. Furthermore, in human hypertension a strong genetic component has been inferred, which has nourished the search for GR-gene mutations in human hypertension.

The Bcl1 polymorphism was originally identified using Southern blot techniques (Murray, Smith, Ardinger, & Weinberger, 1987) and was recently characterized as a G/C transversion 647 base pairs downstream of exon 2, in intron B (Fleury, Beaulieu, Primeau, Sinnett, & Krajnovic, 2003; van Rossum & Lamberts, 2004). Originally, this polymorphism was detected using Southern blotting in combination with the Bcl1 restriction enzyme. Lack of the Bcl1 site due to the polymorphism resulted in a larger band in the Southern blot. This polymorphism was found to be associated with increased corticosteroid sensitivity using a budesonide skin-bleaching test (Panarelli et al., 1998).
<table>
<thead>
<tr>
<th>Region</th>
<th>Position</th>
<th>Nucleotide change</th>
<th>AA change</th>
<th>Characteristics of the hGR-SNP</th>
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<tr>
<td>Promoter</td>
<td>Ex1B−Ex1C</td>
<td>Tth111L-site C → T</td>
<td></td>
<td>Presently not associated with any pathology, may be involved in regulation of basal levels of cortisol, especially detectable at night trough levels. No changes in DST or following other stimulation. Frequency: wt, 40%; heterozygote, 45%; homozygote, 16%.</td>
<td>Detera-Wadleigh, Encio, &amp; Rollins, 1991; Rosmond et al., 2000a; van Rossum &amp; Lamberts, 2004</td>
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<tr>
<td>Exon 2</td>
<td>198</td>
<td>GAG → GAA</td>
<td>Glu22Glu</td>
<td>REL22/23EK = GAGAGG(GluArg)-GAAAAG(GluLys)</td>
<td>Koper et al., 1997</td>
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<tr>
<td>Exon 2</td>
<td>200</td>
<td>AGG → AAG</td>
<td>Arg23Lys</td>
<td>Relative steroid resistance and Dex escape. Lower insulin and lower cholesterol, a more favorable metabolic profile. Male carriers are taller, have more muscle mass, and are stronger. Increased frequency in older population. Decreased risk of dementia. Frequency: heterozygote ± 5–10%.</td>
<td>Koper et al., 1997; van Rossum &amp; Lamberts, 2004; van Rossum et al., 2003a</td>
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<tr>
<td>Exon 2</td>
<td>1220</td>
<td>ATT → AGT</td>
<td>Asn363Ser</td>
<td>Increased cortisol sensitivity to 1 mg Dex, still suppression after 0.25 mg Dex. Associated with strong cortisol response following psychological stress (TSST). Increased BMI and other metabolic disturbances, increased insulin response following Dex. Frequency: heterozygote ± 8%.</td>
<td>Dobson et al., 2001; Di Blasio et al., 2001; de Lange et al., 1997; Huizinga et al., 1998; Koper et al., 1997; Lin et al., 1999a, Wüst et al., 2004</td>
</tr>
<tr>
<td>Intron B</td>
<td>IVS2 + 646</td>
<td>TGATCA → TGATGA</td>
<td></td>
<td>Corticosteroid sensitivity increase in skin bleaching test. Low cortisol levels following the 0.25 mg Dex test. Low HPA axis reactivity psychological stress (TSST), and higher cortisol following lunch. Increased BMI, increased BMI and LDL following overeating (young Swedish population), decreased BMI (elderly Dutch population). Associated with increased blood pressure. Heterozygote frequency ± 30–52%; homozygote frequency ± 0–7%, depending on ethnicity.</td>
<td>Buemann et al., 1997; Detera-Wadleigh et al., 1991; Fleury et al, 2003; Murray et al., 1987; Panarelli et al., 1998; Rosmond et al., 2000b; Stevens et al., 2004; Tremblay et al., 2003; Ukkola, Rosmond, et al., 2001; van Rossum et al., 2003b; Wüst et al., 2004</td>
</tr>
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</table>

Dst, dexamethasone suppression test; Dex, dexamethasone; TSST, Trier social stress test; BMI, body mass index; HPA, hypothalamic–pituitary–adrenal; LDL, low-density lipoprotein.
Recently it was shown that this BclI polymorphisms is a marker of a large allele, or haplotype, spanning almost the entire intron B (+80 kbp), located between exon 2 and exon 3 of the GR gene (Stevens et al., 2004). The gene frequency of this haplotype is between 15 and 33%, depending on ethnicity, making it in potential highly important (Fleury et al., 2003). Watt et al. (1992) described the BclI restriction fragment to be associated with high blood pressure; homozygotes for the larger allele had higher blood pressure scores than homozygotes for the alternative allele (wild types), whereas heterozygotes were intermediates. As described below, in another study of this locus Weaver, Hitman, & Kopelman (1992) reported that the larger allele was associated with severe hyperinsulinemic obesity, a phenotype feature that, in a milder form, is common in patients with essential hypertension.

The N363S polymorphism (Asn363Ser, an AAT-to-AGT transition in codon 363 in exon 2) in the GR gene was originally detected by Koper et al. (1997) and was recently found to be associated with coronary artery disease (CAD), independent of the presence of overweight (Lin, Wang, & Morris, 2003). In addition, unstable angina further increased the association. However, in a previous study by the same group, no such association was detected (Lin, Wang, & Morris, 1999a, 1999b). This has led to fierce debate with respect to the validity of these associations and SNP association studies in general. It has been proposed that functionality of the SNP under study should be revealed through in vitro testing (Daly & Day, 2001; Emahazion et al., 2001; Rosmond, 2003a; Zondervan & Cardon, 2004). Unfortunately, in vitro tests of SNP functionality in cells are also of somewhat limited value, because (a) they exclude the influence of variables from physiology, and (b) the effect of the SNP is heavily dependent on the cellular context (e.g., promoter region, presence of other transcription factors, etc.) (De Bosscher et al., 2003).

### 4.2. Immune Function

Large-scale application of synthetic corticosteroids to suppress rheumatoid arthritis was initially the therapy of choice in the field of autoimmunity. With respect to the molecular mechanism of corticosteroid sensitivity in immune tissue, much research has focused on the GR. GRβ, the putative natural antagonist of GRα, has received the most attention in this field as compared to other GR-gene variants (DeRijk et al., 2002). We described a variant in GRβ to be associated with rheumatoid arthritis and possibly with systemic lupus erythematosus (SLE) (DeRijk et al., 2001). Importantly, this variant was found in vitro to stabilize GRβ mRNA and to increase GRβ expression (Schaaf & Cidlowski, 2002a). It was proposed that this SNP could contribute to the process of autoimmunity by decreasing corticosteroid sensitivity. The expression of the GRβ variant was found to be very low, although several days of exposure of immune cells to cytokines increased the GRα/GRβ ratio to levels at which the dominant activity of the GRβ could become important (Schaaf & Cidlowski, 2002b). In line with this notion is the finding of associations of GRβ expression and corticosteroid resistance in active immune tissue (for overview, see DeRijk et al., 2002). However, in human postmortem hippocampal tissue we detected only very low levels of GRβ expression, as determined by both mRNA expression and immunocytochemistry (DeRijk et al., 2003). Moreover, in this brain region GRβ immune-reactive-positive cells were found to be of bloodborne origin. Thus, at present it is unclear if GRβ plays any role in centrally mediated processes such as behavior or HPA axis regulation.
4.3. Behavior

Although both experimental animal research and studies with human subjects clearly show a profound role of corticosteroids in behavior, few studies have addressed the relationship between GR expression or GR-gene variants and human behavior. An important role of corticosteroid signaling in behavior has been inferred, as described extensively in this chapter; for example, changes in HPA axis reactivity in healthy family members of patients with affective disorders are documented, suggesting a genetic contribution through cortisol regulation (Ellenbogen, Hodgins, & Walker, 2004; Holsboer, Lauer, Schreiber, & Krieg, 1995). Van Rossum and Lamberts (2004) reported in an abstract that carriers of the linked polymorphisms ER22/23EK (GAG AGG [GluArg or ER] g GAA AAG [GlyLys or EK] [Koper et al., 1997]) had a lower risk of dementia as well as fewer white matter lesions in the brain and better performance on psychomotor speed tests. No associations between GR-polymorphisms and psychiatric diseases have been described, although it has to be mentioned that Binder et al. (2004) recently found an association between better treatment efficacy and increased recurrence with a FKBP5, a GR-regulating cochaperone of hsp-90. Psychiatric diseases are considered multigenetic diseases with great environmental influence. Also, little consensus exists with respect to subtle phenotypic determination of psychiatric patients, which is almost a prerequisite to study genetic determinants. Taken together, much attention has to be paid to phenotypic determination and the regulation of the HPA axis in order to minimize variation when studying genetic polymorphisms in psychiatric disorders.

4.4. HPA Axis Regulation

Several GR-gene SNPs have been associated with changes in HPA axis regulation. Human carriers of the Bcl1 polymorphism showed an allele dosage effect; with respect to increased dexamathasone suppression of plasma cortisol (Panarelli et al., 1998; van Rossum & Lamberts, 2004), indicating increased corticosteroid sensitivity in these subjects. The same pattern was found for human carriers of the N363S polymorphism (Huizinga et al., 1998). In contrast, ER22/23EK showed the opposite effect: a decreased sensitivity to dexamethasone and thus a higher postdexamethasone cortisol level (van Rossum & Lamberts, 2004).

Recently, Wüst (2004) showed a strong genetic effect of the N363S and the Bcl1 variant on psychological stress- and ACTH-induced cortisol responses. More precise, carriers of N363S had higher ACTH and cortisol responses following the Trier Social Stress Test (TSST, a psychological stessor) and also higher cortisol following ACTH administration as compared to wild type subjects. Subjects genotyped as Bcl1 heterozygotes had fewer high responses for both cortisol and ACTH following psychological challenge than the N363 carriers, but they were still higher as compared to wild type individuals. Unexpectedly, the Bcl1 homozygotes had lower cortisol responses as compared to wild types, following both TSST and ACTH administration. It is conceivable that the presence of two Bcl1 alleles exceeds a threshold, followed by a downward resetting of the HPA axis, through an unknown mechanism. It is also possible that Bcl1 carriers additionally have ER22/23EK, but too few subjects with this genotype were available.

Interestingly, Stevens et al. (2004), found the Bcl1 site to be in linkage disequilibrium with two other polymorphism both located downstream, showing an allele spanning almost the entire intron B (between exon 2 and exon 3) (see Fig. 4). Still, the molecular
mechanism of this SNP is unknown; it could be that this SNP has an effect on mRNA splicing or stability. An association was established between the presence of this allele and relatively low postdexamethasone (0.25 mg) plasma cortisol levels, compared to noncarriers. These findings indicate that the Bcl1 SNP is associated with a relative increased corticosteroid sensitivity.

The Tth111I variant was found to be located in the promoter region between exons 1b and 1c, 3807 bp upstream of the GR mRNA start site (van Rossum & Lamberts, 2004). Rosmond et al. (2000a) did find an association between this variant and higher total and evening cortisol concentrations, although not with metabolic parameters. In contrast, the group of Lamberts et al. (1996) could not find any association of this polymorphism with dexamethasone-induced cortisol suppression or with antropomorphic markers, cholesterol, glucose, or insulin levels (van Rossum & Lamberts, 2004). As suggested by van Rossum and Lamberts (2004), this discrepancy could be explained by the finding that carriers of ER22/23EK also seem to have the T-variant of the Tth111I site.

Recently we found an allele in the MR gene to be associated with increased saliva and plasma cortisol responsiveness in healthy human subjects during the TSST (DeRijk et al., 2005). However, the full impact of this MR-gene SNP on HPA axis regulation has still to be explored.

Taken together, these data and especially the recent studies by Wüst and Stevens suggest that GR-gene polymorphisms can, by changing the setting and reactivity of the HPA axis, affect peripheral cortisol availability. This will almost certainly have an effect on peripheral tissue reactivity during stress.

4.5. Metabolism

Glucocorticoid effects on metabolism are numerous and complex. In the acute phase, glucocorticoids increase blood glucose by facilitating the flow of substrates through intermediary metabolism and activating the process of gluconeogenesis. AAs are released from skeletal muscle while fatty acids and glycerol are released from adipose tissue. In the liver the enzyme phosphoenol pyruvate carboxykinase (PEP-CK) is induced, resulting in enhanced gluconeogenesis. In addition, peripheral glucose uptake and utilization is inhibited, partly as a result of decreased translocation to the cell surface of GLUT 4 glucose transporters (Barthel & Schmoll, 2003; Reynolds & Walker, 2003). Furthermore, corticosteroids inhibit glucose-stimulated insulin release from pancreatic β-cells, and it has been proposed that cortisol has a regulatory, predominantly inhibitory, effect on plasma leptin concentrations.

Prolonged high levels of glucocorticoids, as opposed to short-term acute elevations, are associated with insulin resistance and peripheral fat depositions. This is most clearly depicted in patients with Cushing’s syndrome, who have high levels of circulating cortisol, often owing to an ACTH-producing tumor. In contrast, patients with Addison’s disease, a deficiency of adrenal cortisol production, are extremely thin and display increased insulin sensitivity.

Human obesity is characterized by excess body fat, whereas the metabolic syndrome describes a constellation of cardiovascular risk factors such as insulin resistance or type 2 diabetes, dislipidemia, and hypertension. It has been proposed that abdominally obese individuals display subtle abnormalities in the regulation of the HPA axis (Rosmond, Dallman, & Björntorp, 1998) and that this dysregulation plays a causative role in the
pathogenesis of human obesity and insulin resistance (Björntorp, 1993). However, additional research has suggested that only minor, if any, changes in the regulation of the HPA axis exist (Seckl, Morton, Chapman, & Walker, 2004). In patients with obesity, levels of cortisol are in fact slightly decreased, probably owing to increased metabolism of cortisol (Stewart et al., 1999). Alternatively, local effects of corticosteroids may result in obesity and the metabolic syndrome.

First, the activity of 11β-HSD type-1, predominantly a 11-ketoreductase, reactivating inert cortisone into cortisol, could be upregulated, resulting in increased corticosteroid efficacy in adipose tissue. In a mouse model exhibiting a two- to threefold overexpression of 11β-HSD type-1 in adipose tissue, modest obesity, glucose intolerance, insulin resistance, dyslipidemia, increased leptin serum levels, and hypertension were observed (Masuzaki et al., 2001). These data suggest that 11β-HSD type-1 activity is involved in the metabolic syndrome, and it is suggested that 11β-HSD type-1 is a pharmacological target in the human metabolic syndrome (Seckl et al., 2004).

Second, GR-gene polymorphism may affect corticosteroid sensitivity of the target tissues. Several studies have found associations of the Bcl1 haplotype with changes in metabolism, including hyperinsulimia, higher abdominal fat, higher body mass index (BMI), higher leptin levels, and greater increases in body weight following experimentally induced overfeeding, in carriers of the C genotype (Buemann et al., 1997; Di Blasio et al., 2003; Rosmond et al., 2000b; Ukkola, Pérusse, Chagnon, Després, & Bouchard, 2001; Ukkola, Rosmond, Tremblay, & Bouchard, 2001; van Rossum et al., 2003b; Weaver et al., 1992). In a long prospective study, the increase in subcutaneous fat over 12 yr was more than doubled in females genotyped as heterozygotes as compared to the wild types and homozzygotes (Tremblay et al., 2003). The same trend was observed in males but did not reach statistical significance. Some controversy about associations can possibly be explained by an age-dependent effect: van Rossum and Lamberts (2004) described a lower BMI in carriers of this genotype with higher age, probably due to increased muscle atrophy (decreased lean mass) in these subjects.

N363S is possibly related to increased corticosteroid sensitivity. Associations have been found with metabolic changes such as higher BMI, waist-to-hip ratio, and insulin response following administration of 0.25 mg dexamethasone (Dobson, Redfern, Unwin, & Weaver, 2001; Huizinga et al., 1998; Lin et al., 1999a). In a severely obese Italian population, the N363S variant was associated with increased BMI (Di Blasio et al., 2003). However, in a Swedish population no such association with either BMI or weight-to-height ratio was found (Rosmond, Bouchard, & Björntorp, 2001), which has led to discussion about the validity of the findings (Rosmond, 2003b). Importantly, in the Swedish study no association was found between the N363S variant and an increased sensitivity towards dexamethasone, in contrast with the previous study by Huizenga et al. (1998). This suggests that the central effects of N363S, e.g., on HPA axis regulation (Wüst et al., 2004), in addition to local tissue-specific effects also play a role in the observed phenotypic changes.

Codons 22 and 23 of exon 2 are possibly related to corticosteroid resistance (Koper et al., 1997). This ER22/23EK polymorphism was associated with a favorable metabolic profile: lower fasting insulin and low-density lipoprotein cholesterol concentrations (van Rossum et al., 2003a). Interestingly, in line with these favorable metabolic parameters, the frequency of this polymorphism was higher in the older population.
Peripheral metabolic status seems to be a factor in the regulation of the HPA axis. Adrenalectomy (ADX) increases the expression of central CRH and other neurotransmitters, probably due to the lack of negative inhibition. Dallman et al. showed that ADX rats drinking saline and glucose appear normal with respect to metabolism and CRH expression (Laugero, Gomez, Manalo, & Dallman, 2002). This suggests that the basal negative feedback signal by corticosteroids on the HPA axis is mediated through peripheral glucose (Dallman et al., 2002). Also, as discussed above, chronic high levels of corticosteroids affect central stress circuits leading to changes in behavior, including increased feeding. It is proposed that chronic stress, as present in western society, leads to increased craving for so-called comfort food, which functions to downregulate central stress systems (Dallman et al., 2003). Indeed, symptoms of depression and anxiety are positively related to anthropometric and metabolic parameters in humans. For example, men with abdominal obesity have symptoms of depression and anxiety (Ahlberg et al., 2002). Moreover, depression (classified according to DSM-IV, not subgrouped in atypical vs melancholic), is associated with increased intra-abdominal fat, resistance to insulin, and impaired glucose tolerance (Roberts, Deleger, Strawbridge, & Kaplan, 2003; Weber, Schweiger, Deuschle, & Heuser, 2000; Weber-Hamann et al., 2002). If depression is further subdivided into melancholic and atypical depression (characterized by lethargy, fatigue, hypersomnia, and hyperphagia), the latter has been found to be associated with low levels of cortisol and probably low levels of CRH and noradrenaline from the Locus Ceruleus (Gold & Chrousos, 2002), suggesting that the hyperphagia functions to downregulate the central stress system. Finally, it was found that plasma glucose levels influence TSST-induced cortisol responses. High levels of glucose, induced by drinking water with 100 g glucose after a night fasting, were associated with much higher saliva cortisol responses as compared to non-glucose-loaded subjects when exposed to the TSST (Kirschbaum et al., 1997).

Although far from clear, there seems to be a bidirectional interaction between the HPA axis and peripheral metabolism. This interaction could have important implications for pathological states such as obesity, the metabolic syndrome, and depression (Eaton, 2002).

5. CONCLUSIONS

Resilience and adaptation seem dependent on the balance of central MR- and GR-mediated actions (de Kloet, 2003; de Kloet et al., 1998). It is thought that the MR activates signaling pathways that stabilize homeostasis by facilitating the selection of a stressor-appropriate coping strategy. On the other hand, the GR represents a mechanism to recover from stress. The receptor activates signaling pathways that facilitate adaptation, in processes such as metabolic demand, immune function, cardiovascular control, and behavior. In the case of behavior, an adequate coping strategy is stored for use at the next encounter. Accordingly, aberrant GR-mediated processes are thought to cause stress-related brain disorders and therefore present targets for therapy. In addition, MR-mediated processes may present an opportunity to design therapeutic approaches for prevention of certain mental diseases.

An aberrant MR/GR balance may lead to a condition of neuroendocrine dysregulation and metabolic, cardiovascular, and behavioral pathology. An additional aspect of aberrant MR/GR balance is a central dysregulation of the HPA axis, which will affect the whole body (Chrousos, Charmandari, & Kino, 2004; de Kloet, 1991; de Kloet et al.,
Many determinants are involved in the MR/GR balance. Bioavailability of corticosteroids and access to their receptors, receptor properties, and numbers as well as the stochiometry with transcription factors and coregulators are important. Moreover, splice variants of the GR gene, GR variants, and SNPs in the GR gene may alter central and local corticosteroid sensitivity. It implies that in case of imbalance the individual loses the ability to maintain homeostasis, if challenged by an adverse event. It is in this arena that the conversion of good vs bad corticosteroid effects may occur. If coping with stress fails corticosteroids fail to optimize stress reactions and targets are exposed to improper corticosteroid concentrations for a prolonged period of time. This condition is thought to sustain reverberating positive feedback loops that further aggravate the condition of imbalance (Gold & Chrousos, 2002).

In addition to genetic influences on the regulation of the HPA axis, traumatic life events can permanently alter the setpoint of the HPA axis (Bremner et al., 2003; Heim et al., 2001; Rinne et al., 2002; Yehuda, 2002; Yehuda, Halligan, Grossman, Golier, & Wong, 2002). It is conceivable that certain GR-gene SNPs modulate the vulnerability to these severe life events and HPA axis regulation with global consequences for metabolism, immune function, cardiovascular regulation, and behavior.

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