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Corticosteroid Receptor Genetic Polymorphisms and Stress Responsivity

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A fundamental question in the neuroendocrinology of stress-related psychopathology is why some individuals florish and others perish under similar adverse conditions. In this contribution we focus on the variants of mineralocorticorticoid (MR) and glucocorticoid receptors (GR) that operate in balance and coordinate behavioral, autonomic, and neuroendocrine response patterns involved in homeostasis and health. In the GR-gene, three single nucleotide polymorphism (SNPs) have been associated with changes in metabolic profile and cardiovascular parameters: the ER22/23EK with a favorable and the N363S and the *Bcl*1 with a more adverse profile. Importantly, the N363S and the *Bcl*1 are found to increase cortisol responses to a psychosocial stressor. As a result, the whole body will suffer from overexposure with possible adverse effects on metabolism, cardiovascular control, immune function, and behavior. Also in the MR gene, variants are being identified that are associated with dysregulated autonomic, behavioral, and neuroendocrine responses. The data suggest that these MR and GR variants contribute to individual differences in resilience and vulnerability to stressors, and that these receptors therefore are potential drug targets for recovery of homeostasis and health.

Key Words: Stress; corticosteroids; corticosteroid receptors; single nucleotide polymorphisms (SNP); vulnerability genes; depression.

Introduction

Any threat to homeostasis activates a network of corticotropin-releasing hormone (CRH) neurons in the limbic-midbrain and triggers the release of the peptide from the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) in the blood *(1,2)*. Subsequently, CRH activates in a coordinate manner the autonomic, physiological, and behavioral adaptations in order to re-establish homeostasis *(1)*. Although CRH is the dominant trigger for the hypothalamic–pituitary–adrenal (HPA) axis activation, resulting in the secretion of corticosteroids from the adrenal glands, its action is potentiated by the hypothalamic co-secretagog arginine vasopressin (AVP). The action exerted by AVP is prominent in adaptation to repeated and chronic stress. The peptides are the driving force of the HPA axis, which displays a circadian rhythm, with high levels just before the active period and low levels before the non-active period and during sleep. In addition, the HPA axis has an ultradian rhythm of about one pulse per hour resulting in phasic release of corticosteroids. During circadian variation and after exposure to a stressor the frequency and amplitude of the pulsatile corticosterone secretion is enhanced *(3)*.

Naturally occurring glucocorticoids, e.g., corticosterone and cortisol, bind to two types of receptor, the high-affinity mineralocorticoid (MR) and the lower-affinity glucocorticoid receptors (GR) (Fig. 1). MR in the kidney regulates electrolyte balance, and, because cortisol and corticosterone are inactivated in the kidney tubular cells by 11beta hydroxysteroid dehydrogenase type 2 (11βHSD-2), this MR is selectively responsive to aldosterone. Peripheral GR are implicated in metabolism, immune suppression, and cardiovascular regulation. In the brain, however, MR and GR are co-localized in abundance in neurons of the limbic brain, particularly in hippocampal neurons of the CA1 and CA2 pyramidal cell field and the dentate gyrus neurons. In these structures, the MR and GR mediate effects on behavioral adaptation and thus also indirectly affect the activity of the HPA axis itself. As a result, a dysregulation of MR and/or GR function will change stress regulation and adaptation with possible adverse implications *(4)* (Fig. 2).

Classically, corticosteroid receptors mediate their effects at the level of the genome by direct transactivation or repression, or by interference with other transcription factors such as AP-1 or NF-κB *(5)*. However, there is also a rapid non-genomic corticosteroid action modulating not only HPA axis activity but also behaviours, although the mechanisms are still poorly understood *(6–9)*. As a consequence, the actions exerted by the steroids proceed in different time domains, e.g., non-genomic vs genomic effects.

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Corticosteroid Receptors

Like all members of the steroid receptor family, three major domains can be distinguished. First, a N-terminal domain, also called the immunogenic domain, harboring receptor-specific transactivational activity. Second, a relatively short DNA-binding domain (DBD) also necessary for homodimerization, and third a C-terminal ligand-binding domain (LBD). The latter is also important for the translocation signal and additional specific transactivational activity. After entry into the cell, the steroid finds the receptor as part of a large heteromeric complex. A key part of the complex is the receptor:HSP90 interaction, which seems to keep the ligand-binding pocket of the receptor in its optimal, high-affinity configuration. Once steroid is bound, the complex disassembles and the "activated" receptor, with the steroidal ligand occupying its site in LBD of the receptor enters the nucleus, a process depending on specific nuclear localization signals *(10)*. Differences in signals involved in translocation of the MR and GR have been described and it has been proposed that the GR is almost exclusively in the cytoplasm while the MR seems evenly distributed between the cytoplasm and the nucleus in the absence of ligand *(10)*. In the nucleus, the receptor interacts with other transcription factors and/or with critical regulatory sites on the relevant genes.

Genetics of the Corticosteroid Receptors

MR and GR Gene

The human mineralocorticoid receptor is located on chromosome 4 (locus 4q31.1) and consists of 10 exons: exon 1α, exon 1β (and possible exon 1γ) and exon 2–9 *(11,12)*. The human glucocorticoid receptor (hGR) gene is located on chromosome 5 (locus 5q31), and also consists of 10 exons *(13,14)*, although very recently many different exon 1's have been described. In addition, a splice variant of the human GR exon 9 exists, designated exon 9β. For both MR and GR genes a similar scheme applies: exon 1 and the first part of exon 2 contain the 5'UTR, exons 2–9 the coding sequences, and most part of exon 9 the 3'UTR *(15)*.

For the human MR gene, two different promotor regions have been described, designated P1 and P2, located just upstream of exons 1α and 1β, respectively *(16–18)*. Specific regulation of exons 1α, β, γ have been observed in the rat hippocampus and is thought to be involved in neuronal sprouting and synaptogenesis *(19)*. During the postnatal development of the HPA axis even a hippocampal-subregion-specific expression of MR mRNA is observed *(20)*. Next to the exon 1 splice variants, a splice variant skipping exons 5 and 6, resulting in a protein of 75 kDa, was found to be a ligand-independent transactivator, and capable of recruiting coactivators *(21)*.

The GR gene promotor region is found to be highly complex. Most upstream (27 kb) is an exon 1A that contains three different splice variants, designated 1A1, 1A2, and 1A3 *(22)*. In addition, more proximal to exon 2, harboring the translation start sites, are exon 1B and 1C *(22,23)*. However, after alignment with the rat exon 1's it has been proposed that even more human exon 1's exist, making a possible total of 12: 1A1–3, 1D, 1E, 1B, 1F, 1G, 1C1–3, and 1H *(24)*. These exons seem to have their own promotors and specific tissue expression, giving rise to cell-specific expression of the GR *(13,25,26)*. Interestingly, it has recently been reported that these different exons give rise to alternative splicing with acceptor sites behind the first ATG in exon 2. The results were N-terminal truncated proteins, which, however, were found to be transcriptionally active *(27)*. Moreover, the group of Cidlowski described multiple protiens (GR-A to GR-D) arising from alternative translation initiation sites with MW of 94, 91, 82–82, and 53–56 kDa *(25, 28,29)*. These proteins were also transcriptionally active and showed unique gene-regulation profiles of target genes. For the human MR, two alternative translation variants, MR-A and MR-B, were found, with different transcriptional activities *(30)*.

Several more splicing variants have been described, including the GR-P, GR-γ, and GRβ, the latter will be discussed in the section on immune function. The GR-P (or GR-δ) results from an alternative splicing event in which exon 8 is replaced by intron G, giving rise to a truncated protein (676 AA) *(31)*. This GR-P seems to be present in several freshly isolated hematological tumor cells from different donors, suggestive of wide-spread expression *(32–34)*. No ligand binding is observed in this variant due to lack of exons 8–9; however, this variant could play a role in corticosteroid sensitivity of tumor cells. The GR-γ was found to be the result of the usage of an alternative mRNA splicing site, and an additional codon, GTA coding for arginine, was found to be inserted between exons 3 and 4, at AA 452 *(35)*. hGR-γ seems rather ubiquitously expressed while its function is presently unknown.

This example of one gene, the GR, showing complex regulation and coding for multiple proteins can at least partly explain the numerous and diverse physiological responses elicited by corticosteroid hormones.

Single Nucleotide Polymorphism

Mutations often consist of premature stop codons, deletions, inserts, abnormal splicing, or amino acid changes resulting in severe clinical phenotypes. Mutations in the human MR gene resulting in decreased function are associated with hypertension or pseudohypoaldosteronism (PHA1), a rare form of mineralocorticoid resistance characterized by salt loss, dehydration, vomiting, and failure to thrive *(36,37)*. The phenotype is rather heterogeneous, ranging from severe forms with poor clinical outcome to milder forms in which treatment can be discontinued. In addition, genetic disruption of the MR in mice (MR–/– mice) results not only in salt waisting, but also in specific loss of granule cells the hippocampus possibly because of reduced neurogenesis *(38)*,

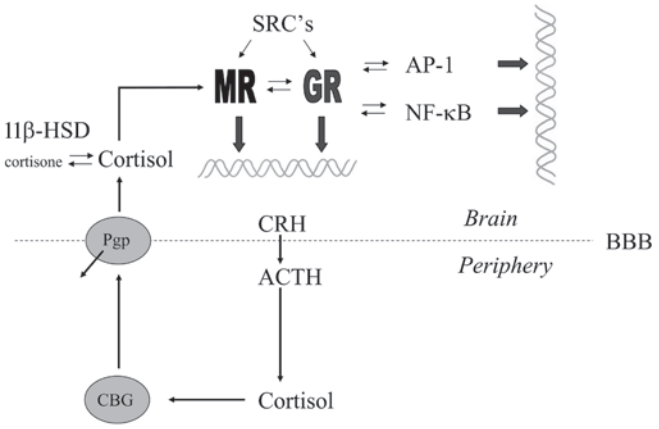

Fig. 1. Factors involved in corticosteroid signaling. Upon stimulation of the HPA axis, CRH induces the release of ACTH from the pituitary gland and cortisol is secreted from the adrenal glands in the circulation. Up to 95% of cortisol binds corticosteroid binding globulin (CBG), thereby protecting the hormone against degradation by liver P450 enzymes. At the level of the blood brain barrier (BBB), P-glycoprotein (Pgp) can hamper access of cortisol to the brain. In the target tissue, cortisol can be converted to the inert cortisone by 11β-HSD type 2 or reactivated by 11β-HSD type 1. At the receptor level, the amount, degree of phosphorylation, and affinity 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, the GRα *(80,94)*. In addition, many translation variants exist, the GR-A, B, C, and D, as a result of usage of different translation start sites *(27–29,68)*. The GR-B seems to be even more active as compared to the classic GR(α)-A. For the MR, two variants have been detected, the MR-A and MR-B *(30)*. 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, the 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 *(5)*. These activities are important in immune function, in cardiovascular control, in growth and development and in behavior. Finally, chromatin/DNA structure, modulated by histones or methylation, and nature of the corticosteroid responsive elements determines efficacy of transcriptional control *(95,96)*.

indicating the importance of the MR also in neuronal integrity (Fig. 1). In contrast to MR loss of function, activating MR mutations can result in hypertension, exacerbated by pregnancy *(39)*. One such mutation, the S810L, resulted in an MR in which other steroids such as progesterone, normally MR antagonists, become potent agonists. This resulted in overactivation of the MR, predominantly during pregnancy with high levels of progesterone.

Mutations within the GR gene are also often not compatible with life, and the corticosteroid-resistance syndrome is characterized by hypertension, excess androgens, and increased plasma cortisol concentrations in the absence of the stigmata of Cushing's syndrome *(40–43)*. Furthermore, several GR gene mutations have been found in human malignancies including Cushing's disease; for review see ref. *41*. Next to mutations, naturally occurring MR and GR gene polymorphisms, single nucleotide polymorphism (SNPs) have been found, not directly associated with overt disease. However, the distinction between mutations and SNPs is often not clear, and it is difficult to define a SNP. Currently, most SNPs are available from the internet (e.g., http://www.receptors.org/cgi-bin/nrmd/nrmd.py) and almost on a daily base new SNPs are added or changed. In the next section we will discuss some of the most studied SNPs in the MR and GR gene. When studying associations between SNPs and phenoptypes, several important issues emerge. SNPs are often linked forming an allele, making it unclear if the association is due to the SNP used as the "tag" *(44)*. To overcome possible "false positive" associations, showing functionality of an SNP can help: first it shows which SNP is indeed causative to the association, while second, elucidation of the functionality could explain the result or fit into the original hypothesis.

Metabolism

Cortisol has a pronounced effect on glucose metabolism by both decreasing glucose utilization and increasing glucose availability. Prolonged high levels of glucose are associated with insulin resistance and peripheral fat depositions, while cortisol has a strong regulatory, predominantly inhibitory, effect on plasma leptin concentrations. It has been hypothesized that hyperactivity of the HPA axis may play a causative role in the pathogenesis of human obesity and insulin resistance *(45)*. Human obesity is characterized by excess body fat, while abdominally obese individuals have also been shown to display abnormalities in the regulation of the HPA axis *(46)*.

Several GR gene SNPs have been tested for associations with obesity or the metabolic syndrome (Fig. 2). For instance, the so-called *Bcl*1 polymorphism, originally identified using Southern blot techniques *(47)*, was related to increased corticosteroid-sensitivity (budesonide skin bleaching) *(48)* and was only recently characterized as a G/C transversion 647 basepairs downstream of exon 2, in intron B *(49,50)*. The gene frequency of this haplotype is fairly high, between 15% and 33% of the minor allele (G) depending on ethnicity, making it potentially highly important *(49)*. The mechanism of this important SNP has not been elucidated yet. Several studies have found associations of this haplotype with changes in metabolism including hyperinsulimia, higher abdominal fat, higher body mass index (BMI), higher leptin levels, and larger increases in body weight following experimentally induced overfeeding, in carriers of the C genotype *(50–56)*. In a prospective study over 12 yr, the increase in subcutaneous fat was more then doubled in females genotyped as heterozygotes as compared to carriers of the major allele homozygotes of the minor allele *(57)*. The same trend was observed in males, but did

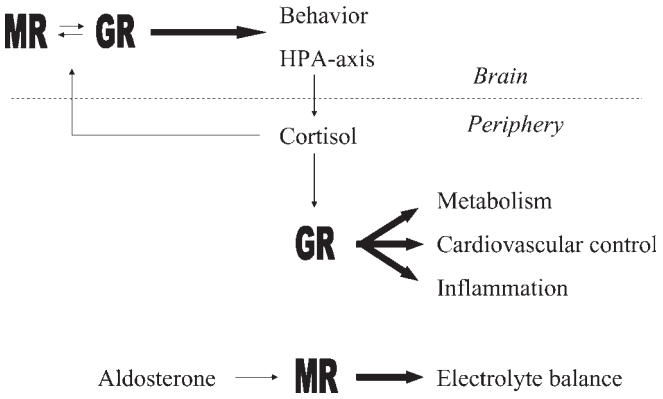

Fig. 2. Levels of control exerted via MR and GR. In the periphery, glucocorticoids mediate metabolic, cardiovascular, and inflammatory control through the GR. The MR in the kidney is responsive to aldosterone, owing to inactivation of cortisol to cortisone, and is involved in electrolyte balance. Brain MR and GR, however, are both responsive to cortisol, where they mediate behavioral and HPA axis regulation in reaction to stressors. A dysregulation of MR/GR-mediated control of these central stress responses will lead to maladaptive cortisol levels with effects on metabolic, cardiovascular, and inflammatory control. Single nucleotide polymorphisms (SNPs) that affect central MR- and GR-mediated processes such as HPA axis control (e.g., the N363S or *Bcl*1), are expected to represent a vulnerable phenotype by introducing a bias towards stress-related disorders after adverse experiences.

not reach statistical significance. Some controversy about associations can possible be explained by an age-dependent effect: van Rossum et al. described a lower BMI in older subjects, probably due to increased muscle atrophy in carriers of this genotype *(58)*.

The Asn363Ser (N363S, an AAT to AGT transition in codon 363 in exon 2) GR gene SNP was originally detected by Koper et al. *(59)*, and possibly related to increased corticosteroid sensitivity. At this moment, no data are available describing the molecular mechanism of this important GR gene SNP. Just like the *Bcl*1 allele, associations in carriers of the minor allele (serine at position 1220, frequency from 3% to 7%) have been found with metabolic changes such as a higher BMI, waist to hip ratio, and a higher insulin response following 0.25 mg dexamethasone *(60–62)*. In a group of French type 2 diabetic patients, higher body weight was also found, although the frequency of serine carriers (the minor allele) was not different from a non-diabetic group, indicating no contribution in the ethiology of diabetes *(63)*. In a group (n = 295) of South Asians living in the UK, a much lower frequency of this polymorphism was found (only 0.3%), making it unlikely that this SNP contributes to the prevalence of the metabolic syndrome in this ethnic group *(64)*, indicating that the genetic background is important. Also in a severely obese Italian population, the N363S variant was associated with increased BMI *(56)*. However, in a Swedish population no such association with either BMI or WHR was found *(65)*, which has led to discussion about the validity of the findings *(66)*. Importantly, in this latter Swedish study no association was found between the N363S variant and an increased sensitivity toward dexamethasone, in contrast with the previous study by Huizenga et al. *(62)*. This suggests that the central effects of the N363S, e.g., on HPA axis regulation *(67)*, could be a prerequisite for the peripheral tissue effects.

The codons 22 and 23 of exon 2 (GAG AGG [GluArg or ER] → GAA AAG [GlyLys or EK]) show linked polymorphisms originally detected by Koper et al., and are possibly related to a relative corticosteroid resistance *(59)*. Recently, Koper et al.'s group reported that this SNP determines the balance of translation efficacy of the two ATG start codons in exon 2, the first at codon 1 and the second at codon 27 *(68)*. The presence of the SNP, that is the GAA AAG form, resulted in increased expression of GR-A, perhaps as a result of changed secondary structure of the mRNA. In this study it was also found that the GR-A was transcriptionally less active, resulting in an overall mild corticosteroid resistance, in line with a previous report *(29)*. This ER22/23EK polymorphism was associated with a relatively favorable metabolic profile: lower fasting insulin and LDL cholesterol concentrations *(69)*. The effects were found to be gender and age-dependent: in middle aged males (36 yr) carriers were taller, had more lean mass, and more muscle mass and strength as compared to non-carriers *(70)*. These differences were not seen in children or adolescents. In woman, no differences in BMI were found, although waist and hip circumferences tended to be smaller. Interestingly, in line with these favorable metabolic parameters, the frequency of this polymorphism is reported to be higher in the older population (78 yr) next to lower levels of C-reactive protein *(71)*, although this finding has to be confirmed by other studies.

Cardiovascular Controls

The balance of salt, water, and blood pressure is regulated to a large extent through aldosterone acting on the MR. Several mutations/SNPs are found to affect these functions as described above. As part of the search for the molecular mechanism behind PHA1, several groups sequenced the MR gene and detected multiple SNPs *(72,73)*. Some SNPs have been tested for functionality, showing changes in DNA binding, ligand binding and transcriptional activity *(74)*.

Next to aldosterone and MR, glucocorticoids have been associated with increased vascular tone and cardiac output. Watt et al. described the *Bcl*1 restriction fragment to be associated with high blood pressure *(75)*; homozygotes for the larger allele had higher blood pressure scores than contrasting homozygotes for the alternative allele, while heterozygotes were intermediates. As described above, in another study of this locus, Weaver et al. reported that the larger allele was associated with severe hyperinsulinemic obesity *(51)*, a phenotype feature that, in a milder form, is common in patients with essential hypertension.

The GR gene SNP N363S was found to be associated with coronary artery disease (CAD), independent of overweight *(76)*. In addition, unstable angina further increased the association. In another study by the same group, no such association was detected *(60,77)*. However, elucidation of the molecular background of the N363S could help to strenghten this assocation as would retesting in a different cohort.

Immune Function

Corticosteroids are widely used to treat inflammatory diseases, while it is assumed that endogenous corticosteroids as released during immune activation and inflammation play an important role in regulating these processes *(78,79)*. One of the first applications of steroids was in the field of autoimmunity: the usage of synthetic corticosteroids to suppress rheumatoid arthritis. Of all the GR-gene variants the GRβ has received most attention in this field *(41,80)*. A variant in the 3' UTR of the human GR exon 9 was described and found to be associated with rheumatoid arthritis and possibly with SLE *(81)*. This variant, an A to G change at the first A in the ATTTA sequence, resulted in vitro in stabilization of GRβ mRNA and subsequently in an increased GRβ expression *(82)*. The expression of the GRβ variant was found to be very low, although several days of exposure of immune cells to cytokines increases the GRα/GRβ ratio to levels in which the dominant activity of the GRβ could become important *(83)*. It was proposed that this SNP could contribute to the process of autoimmunity by decreasing corticosteroid sensitivity. In line with this notion is the finding of associations of GRβ expression and corticosteroid resistance in active immune tissue *(41)*, and the recently found association between this SNP and decreased infection with *Staphylococcus aureus (84)*.

HPA Axis Regulation

Regulation of HPA axis responsiveness is highly complex and it is now clear that different stressors lead to different patterns of HPA-axis responses and adaptations *(4, 85,86)*. Therefore, many different tests and paradigms have been developed to test these specific aspects of the HPA axis. For example, using the dexamethasone suppression test, acting at the pituitary to inhibit ACTH release, Panarelli et al. found increased suppression in carriers of the *Bcl*1 polymorphism *(48,58)*. This is indicative of increased corticosteroid sensitivity. In addition, Stevens et al., found the *Bcl*1 site to be in linkage disequilibrium with two other polymorphisms both located downstream, showing an allele spanning almost the entire intron B (between exon 2 and exon 3) *(87)*. Even more importantly, an association could be established between this allele and relative low post-dexamethasone (0.25 mg) plasma cortisol levels. These findings strengthen the association of the *Bcl*1 SNP with a relatively increased corticosteroid sensitivity. The same pattern was found for the N363S polymorphism *(62)*, using 1 mg and 0.25 mg dexamethasone. In contrast, the ER22/23EK showed the opposite effect: a decreased sensitivity to dexamethasone and thus a higher post-dexamethasone cortisol level *(58)*.

Using a psychosocial stressor, Wüst et al. showed strong genetic effects of the N363S and the *Bcl*1 variant on HPA axis responsivity *(67,86)*. Carriers of the N363S had higher ACTH and cortisol responses, after exposure to the stressor and higher cortisol levels following ACTH administration as compared to "wild-type-type" subjects. Subjects genotyped as *Bcl*1 heterozygotes had less high responses, both for cortisol and ACTH following the psychological challenge than the N363 carriers, but they were still higher as compared to "wild-type-type" individuals. Unexpectedly, the *Bcl*1 homozygotes had lower cortisol responses as compared to controls, both following the psychological stressor and ACTH administration. This is the more remarkable because homozygote carriers of this minor allele also had the phenotype of the "wild-type-types" with respect to changes in metabolic profile *(57)*; see section on metabolism. It is conceivable that the presence of two *Bcl*1 alleles exceeds a threshold, followed by a downward resetting of the HPA axis and/or metabolic effects, through an unknown mechanism. Unfortunately, too few subjects with the ER22/23EK genotype were available to test the impact of this polymorphism on HPA axis reactivity.

The Tth111I variant was found to be located in the promotor region upstream of exon 1c, 3807 bp upstream of the first translation start site in exon 2 *(58)*. The group of Lamberts et al. could not find any association of this polymorphism with dexamethasone-induced cortisol suppression or with anthropomorphic markers, or cholesterol, glucose, or insulin levels *(58)*. In contrast, Rosmond et al. did find an association between this variant and higher total and evening cortisol concentrations, although not with metabolic parameters *(88)*. As suggested by van Rossum et al., this discrepancy could be explained by the finding that the ER22/23EK is linked to the T variant of the Tth111I site (3% of the population), while 12% of the population is carrier of the Tth111I site without the ER22/23EK *(58)*.

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

Behavior

Changes in HPA axis reactivity in healthy family members of patients with affective disorders are documented, suggesting a genetic contribution through cortisol regulation *(89,90)*. In post-traumatic stress disorder (PTSD) patients, increased reactivity of the HPA axis and increased corticosteroid sensitivity has been inferred *(91)*. In 118 Vietnam War veterans, the frequency of the N363S or *Bcl*1 was

not different from control subjects ($n = 42$) *(92)*. However, no differences were observed in corticosteroid sensitivity as assessed using the 0.25 mg DST, which makes drawing of clear conclusions difficult. In an abstract, Van Rossum et al. recently reported that ER22/23EK carriers had lower risk of dementia as well as fewer white matter lesions in the brain and better performances on psychomotor speed tests *(58)*.

A role for the GRβ, and its SNP in exon 9β, the A to G transversion, in behavior and neuroendocrine control is at present also unclear. We measured GRβ expression in human post-mortem hippocampal tissue by both mRNA expression and immunocytochemistry, but only found very low levels of mRNA of the GRβ isoform *(92)*. Moreover, in this brain region GRβ-immune reactive positive cells were found to be of blood-borne origin. Thus, at present it is unlikely that the GRβ plays an important role in central mediated processes such as behavior or HPA axis regulation.

Concluding Remarks and Future Directions

The identification of MR and GR variants has important implications for the role of these receptors in the maintenance of health and homeostasis *(4,93)*. Current evidence suggests that the MR activates signaling pathways aimed *to prevent* disturbance of homeostasis by facilitating the selection of an appropriate behavioral response to deal with a challenge. The GR represents a mechanism *to recover* from stress. GR mediates the action of cortisol on signaling pathways aimed to facilitate behavioral adaptation and to store an adequate coping strategy for use at the next encounter. Here any impairment in one receptor, resulting in a different secretion of corticosteroids, will lead to over or under exposure to corticosteroids of the other receptor. These MR- and GR-mediated variants may therefore make up an important component of the genetic mechanisms that govern individual differences in coping with stress, resilience and vulnerability to disease. In addition, these aberrant MR- and GR-mediated processes may present targets for prevention of and recovery from stress-related psychopathology.

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