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Therapy Insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression?

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SUMMARY

In severely depressed patients, emotional arousal, cognitive abnormality and vulnerability to psychotic episodes are linked to a hyperactive hypothalamic–pituitary–adrenal (HPA) axis and high levels of circulating cortisol. The susceptibility pathways underlying these disturbed brain functions are influenced by genetic factors, early-life priming experiences and later-life events. Cortisol is an important determinant in this so-called three hit model. The action of cortisol is protective, but can become harmful if exposure of susceptibility pathways to the stress hormone is excessive and sustained or inadequate. In this article we argue that this change in role of cortisol from protective into harmful depends on the functioning of the mineralocorticoid and glucocorticoid receptors and the context in which the organism experiences the stressor. Actions mediated by the mineralocorticoid and glucocorticoid receptors are complementary and operate in different time domains of the stress response: the mineralocorticoid receptor normally prevents stress-induced disturbances, but if such disturbances occur the glucocorticoid receptor helps the recovery process. An imbalance in these receptor-mediated actions is thought to increase vulnerability to stress-related psychiatric disorders in predisposed individuals. Correction of the imbalance between the mineralocorticoid receptor and the glucocorticoid receptor can, therefore, facilitate recovery processes still present in the diseased brain, provided that the right psychological context is offered to the individual.

KEYWORDS brain, depression, glucocorticoids, mineralocorticoids, stress

REVIEW CRITERIA

PubMed was searched using the terms "stress", "adaptive behaviour", "brain", "cortisol", "mineralocorticoid receptors", "glucocorticoid receptors" and "mood disorders" between 1996 and 2006. We also searched the reference lists of identified articles for further papers.

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INTRODUCTION

Depression occurs in various degrees of severity ranging from just feeling 'down' towards a full-blown clinical condition characterized by distorted thought and despair. According to a study by the WHO, clinical depression is a leading cause of disability worldwide.[1] Depressive conditions are recurrent and can be comorbid with heart disease, osteoporosis and abdominal obesity.[2,3] The current antidepressant drugs provide an effective treatment of the symptoms of depression, as is shown by the selective inhibitors of serotonin reuptake and norepinephrine reuptake. These drugs are more selective and have fewer side-effects than their prototype tricyclic antidepressants discovered by serendipity some 50 years ago.[4]

How the current drugs exert their therapeutic action is still poorly understood. For instance, the serotonin reuptake inhibitors rapidly promote neurotransmission mediated by serotonin (5-hydroxytryptamine), but it takes several weeks to improve the clinical condition of depressed patients. In addition, there is little understanding of the pathogenic mechanism underlying depressive illness. A meta-analysis of epidemiological studies that included twins indicated that depression has an estimated heritability of 37%.[5] Individuals who have experienced 'priming' by an early-life trauma, such as parental loss or sexual or physical abuse, could also present a vulnerable phenotype.[6,7] This vulnerability of traumatized individuals might depend on genetic variation of the serotonin reuptake transporter, particularly in young, depressed patients,[8] but generally depression is thought to have a multifactorial polygenic cause.

These findings raise the question of how genetic factors and early-life priming experiences increase susceptibility to stressful events in precipitating depression. The question calls for a mechanism underlying vulnerability to depression rather than identification of the disease genes per se. Crucial for understanding

the mechanisms controlled by these genetic and environmental interactions is the hypothalamic–pituitary–adrenal (HPA) axis, which coordinates experience and behavior with the secretion of its hormonal end product: cortisol in primates and corticosterone in rodents. These corticosteroids regulate HPA axis activity by feedback control of hypothalamic corticotropin-releasing-hormone (CRH)-producing neurons and pituitary adrenocorticotropic hormone release. Corticosteroids also have notable actions on the neural pathways projecting to the CRH neurons from distant limbic–midbrain and cortical brain regions—the hippocampus, amygdala and prefrontal anterior cingulate cortex (Figure 1). In these regions corticosteroids can alter the function of neuronal networks underlying the control of mood and memory processes through activation of the mineralocorticoid receptor and glucocorticoid receptor.[9]

In this article cortisol and its two brain receptor types are proposed as proximal factors in vulnerability to depression. We argue that modulation of cortisol signaling in these brain regions is a potential treatment option to reduce susceptibility to stress-related psychiatric illness and to promote a recovery mechanism that is still present even in the diseased brain.

ROLE OF THE HPA AXIS AND CORTISOL IN DEPRESSION

The arguments to link a vulnerable phenotype for depression with the HPA axis and cortisol are based on the following lines of evidence. First, in vulnerable phenotypes the major stressors that activate the HPA axis and increase cortisol secretion commonly precede the onset of depression, although stressors are not always necessary as triggers.[10]

Second, increased and sustained HPA axis activation is observed in about 50% of severely depressed patients, even under a common daily burden. This feature is demonstrated, for example, by the flattened circadian rhythm of cortisol, particularly because of elevated trough levels in the evening.[11,12] Furthermore, CRH levels are increased in cerebrospinal fluid and in the postmortem paraventricular nucleus of depressed patients.[13] Endocrine challenge tests, such as the combined dexamethasone plus CRH test, reveal that normalization of HPA axis regulation is a prerequisite for successful antidepressant treatment, whereas HPA dysregulation precedes relapse, particularly in individuals with a high genetic susceptibility.[14]

Third, as an extension of the second argument, even though depressed patients with hypercortisolemia rarely develop the overt phenotype of Cushing's syndrome, milder physical signs of excess cortisol are common.[3] Verbal memory tests show disturbed focus, attention and encoding rather than disturbed memory recall per se.[15]

Fourth, the risk for depression and steroid psychosis is increased during Cushing's syndrome as well as during long-term pharmacotherapy with potent synthetic glucocorticoids. These symptoms of depression generally disappear upon cessation of glucocorticoid excess, surgical removal of the cortisol-producing tumor or antiglucocorticoid administration.[16] However, chronically high cortisol levels appear related more to emotional arousal, psychotic disorganization and cognitive impairment than to depressive illness as such.[11,17]

Fifth, variations in genes coding for proteins involved in corticosteroid receptor signaling are associated with recurrence of depressive episodes and the response to antidepressant drugs.[18,19]

Collectively, the data suggest that rapid activation of the HPA axis is essential for health as long as it is turned off efficiently. Hence, a chronically hyperactive HPA axis and elevated cortisol levels increase vulnerability to severe depression and psychotic episodes. Important questions are the proximal cause of increased HPA axis activity and how cortisol action, which is essential for life, health and adaptation, can change from a protective into a harmful signal.

THE CORTICOSTEROID RECEPTOR HYPOTHESIS OF DEPRESSION

Stressful life events can undoubtedly precipitate depression in predisposed individuals carrying genetic and experience-related vulnerabilities. In such predisposed individuals increased HPA axis activity can result from overactive hypothalamic CRH neurons and/or resistance to corticosteroid feedback.[11,13,20,21] This resistance can be caused by reduced access to the receptor.[22,23] The most profound impact is, however, caused by deficits in the function of the receptor per se or by impaired regulation of corticosteroid-responsive genes, particularly in a context of excessive stimulation by stress.[9,11] Impaired receptor functioning attenuates

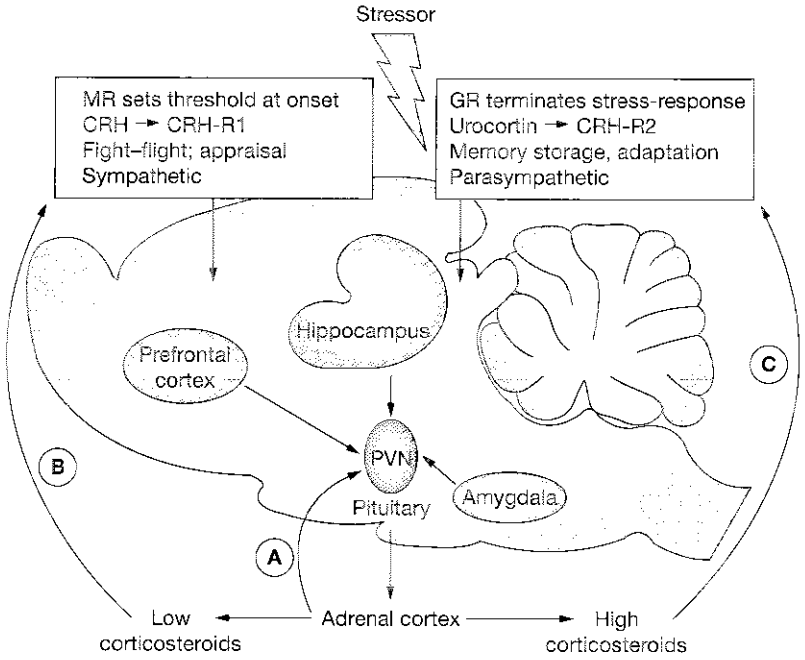

Figure 1 The brain as regulator and target of corticosteroids. (**A**) Stressful stimuli stimulate, through afferent pathways, the CRH and vasopressin neurons in the PVN that orchestrate behavioral, autonomous and neuroendocrine response patterns.[90] Physical stressors (e.g. pain, blood loss, heat and cold) directly stimulate the PVN via ascending aminergic pathways. Psychological stressors require processing in limbic–cortical brain structures (e.g. hippocampus, amygdala and prefrontal cortex) that communicate transsynaptically with the PVN. The neuroendocrine response pattern enhances the secretory bursts of cortisol (primates) or corticosterone (rodents) from the adrenal cortex. The corticosteroids feed back on the brain circuits that have produced their own secretion and prevent them from overexcitation.[9,24,77] These actions exerted by the steroids are mediated by (**B**) MRs and (**C**) GRs. Under psychosocial stress conditions MRs set the threshold at the onset of the stress response by facilitating appraisal processes, which—through CRH-R1—determine the extent of CRH action on HPA activation, sympathetic nervous system responses and fight–flight behavior. The rising corticosterone levels after stress progressively activate GRs, which facilitate adaptation, promote memory storage and hence prepare for coping with future events. CRH-R2 activation by urocortins and parasympathetic nervous activity is thought to synergize with GRs to promote recovery.[9] MRs and GRs operate in complementary fashion through a (non)genomic mechanism to facilitate adaptation; imbalance is thought to enhance vulnerability to stress-related psychiatric illness. Abbreviations: CRH, corticotropin-releasing hormone; CRH-R1, CRH receptor 1; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PVN, paraventricular nucleus.

Box 1 Characteristics of mineralocorticoid and glucocorticoid receptors

Mineralocorticoid receptors

- Restricted to limbic neurons—hippocampus, septum and amygdala
- High affinity for corticosterone and cortisol
- Low affinity membrane receptor
- Promiscuous; bind naturally occurring glucocorticoids, mineralocorticoids aldosterone and deoxycorticosterone, and progesterone
- Substantially occupied, even under basal resting conditions

Glucocorticoid receptors

- Widely expressed in limbic–cortical brain structures, glial cells and neurons
- Tenfold lower affinity for cortisol and corticosterone
- Selective for synthetic and naturally occurring glucocorticoids
- Progressively occupied after stress and during the ultradian or circadian rise

corticosteroid feedback, resulting in cortisol responses of large magnitude and long duration. Locally, these cortisol actions can be amplified by 11β-steroid dehydrogenase.[22]

A crucial factor is that the actions exerted by cortisol are mediated in the brain by the high-affinity mineralocorticoid receptor and lower-affinity glucocorticoid receptor (Box 1, Figure 1).[9] Studies done over the past two decades have demonstrated that homeostatic control appears dependent on coordinated and complementary actions of cortisol mediated by these two receptor types. The following modes of operation of these receptors can be distinguished.

First, in the initial phase of the stress reaction cortisol increases attention, vigilance and emotional responses.[24,25] The hormone also regulates neuronal circuits underlying perception and appraisal of the stressful situation, while facilitating selection of the appropriate behavioral response to deal with the stressor. The mineralocorticoid receptors in the limbic brain appear to mediate these actions. It has been discovered that the receptor acts initially at the membrane level in coordination with excitatory responses and subsequently by regulation of gene transcription. Both the fast responses on excitatory transmission and the slower ones are suppressed after administration of antimineralocorticoids.[26]

Second, in later phases of the stress response, when the circulating cortisol levels increase further, the lower-affinity brain glucocorticoid receptors become increasingly occupied. The action mediated by the glucocorticoid receptor facilitates termination of the stress response

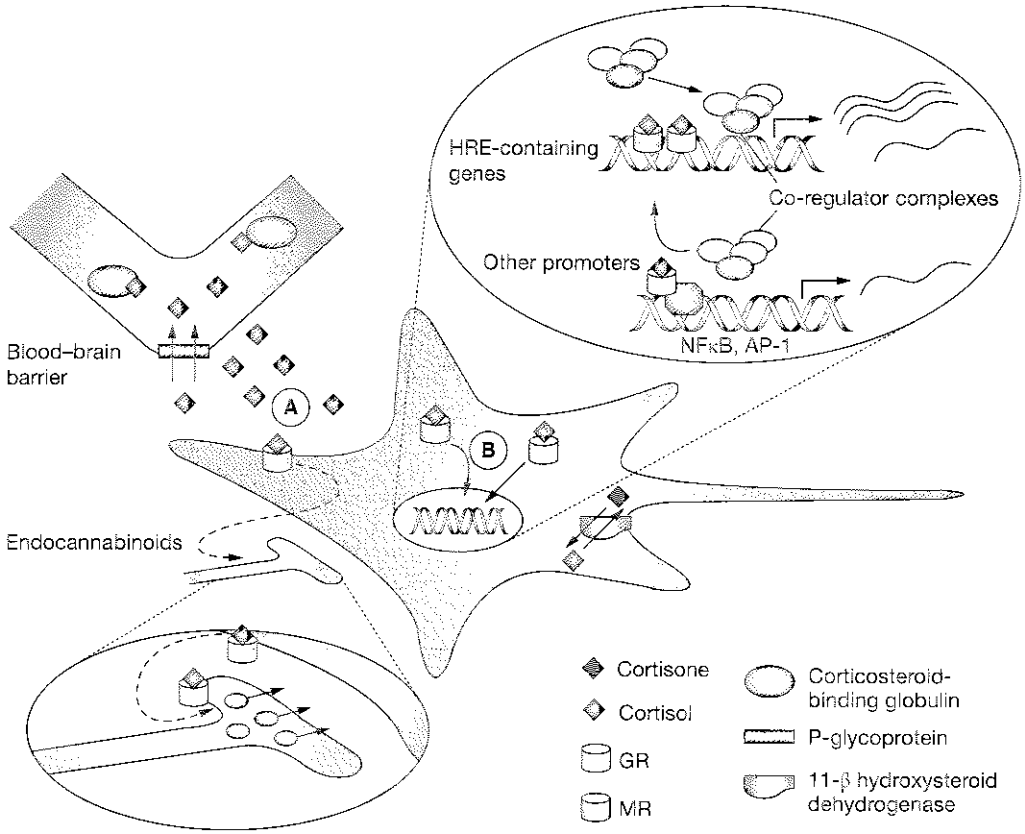

Figure 2 Mechanism of action of glucocorticoid hormones and potential drug targets. Cortisol modulates—via activation of both MRs and GRs—cellular functions and membrane and genomic responses over a time span from seconds to hours. (**A**) Membrane responses include rapid modulation of the release of the excitatory glutamate transmitter either directly or trans-synaptically.[26,27] (**B**) The genomic mechanisms via MRs and GRs involve translocation to the nucleus after hormone binding. Stimulation or repression of transcription occurs via direct DNA binding of the receptors to HREs in regulatory regions of target genes or by interfering with other transcription factors, in a manner that is independent of DNA binding of the steroid receptors themselves, and repressing gene activation by these other transcription factors. Ligand availability is determined, apart from adrenal output, by corticosteroid-binding globulin, P-glycoprotein and 11β-hydroxysteroid dehydrogenase. Abbreviations: AP-1, adapter-related protein complex 1; GR, glucocorticoid receptor; HRE, hormone-response element; MR, mineralocorticoid receptor; NF-κB, nuclear factor κB.

and promotes recovery by mobilization of energy resources. At the same time, other information unrelated to the initial stressor is suppressed.[24,25]

Third, the glucocorticoid receptor promotes memory storage of the appropriate behavioral response to deal with the stressor and eliminate behavior that is no longer relevant. Accordingly, cortisol action through the brain glucocorticoid receptors promotes behavioral adaptation, and thus helps to prepare for future events.[9] This action of cortisol provides stability or homeostasis through adaptive changes, a process also called allostasis.[20] Most known actions mediated by the glucocorticoid receptor involve regulation of gene transcription, but fast, membrane-mediated effects involving cannabinoids have also been described (Figure 2).[26,27]

For maintenance of homeostasis and health it is a prerequisite that the actions mediated by the mineralocorticoid and glucocorticoid receptors operate in the appropriate temporal domain and context of the stressful situation.[24,25] If the stress signals act at inappropriate times and thus are out of context, information processing is impaired, causing abnormalities in cognitive performance and behavioral adaptation. These effects are hallmarks of depression.[9] Accordingly, the corticosteroid receptor hypothesis states that once the balance in actions mediated by

the mineralocorticoid receptor and the glucocorticoid receptor is disturbed, the individual loses the ability to maintain homeostasis if challenged, for example by experiencing an adverse life event.[9,11] Such disturbances in balance can lead to a condition of neuroendocrine dysregulation and impaired behavioral adaptation as a risk factor for the precipitation of depression.

MATURATION OF SUSCEPTIBILITY PATHWAYS IN VULNERABLE PEOPLE

The 'three hit' model suggests that genetic susceptibility and early-life priming experiences influence responses to stress triggers such that they can precipitate depression. Clinical studies addressing the role of corticosteroids in this model are directed towards, for example, the identification of single-nucleotide polymorphisms (SNPs), either in candidate genes or genome-wide, and associating such candidates with a specific endophenotype. Candidate genetic susceptibility factors and progress in understanding the effects of early-life priming experiences and the role of stress triggers in humans and animal models are described below; the models mimic aspects of the etiology and pathophysiology of depression. Core symptoms of depression are anhedonia (a loss of interest or pleasure in daily activities) and behavioral despair (the inability to cope with stressful experiences); both symptoms can be modeled in animals. Depression must, however, be recognized as consisting of a wide variety of symptoms and disease states. The illness has a variable course and severity and there are no clear diagnostic tests. Nevertheless, a dysregulated HPA axis is a common denominator in many patients, particularly during psychotic episodes.

Genetic susceptibility factors

Individuals carrying the ER22/23EK SNP in exon 2 of the glucocorticoid receptor gene have a favorable treatment outcome for depression (Figure 3).[19] Such individuals seem to have a healthier metabolic profile and better cognitive function than the general population and resistance to cortisol.[28] By contrast, individuals with other functional polymorphisms in the glucocorticoid receptor gene displayed an enhanced adrenocorticotropic hormone and cortisol response to a psychosocial stressor than do controls.[29] Several SNPs have also been identified in the mineralocorticoid receptor gene and carriers of the common mineralocorticoid receptor I180V variant showed enhanced cortisol and heart-rate responses to a psychosocial challenge. A weak association of this SNP with depression (measured on the geriatric depression scale) was found in an elderly population aged 80–85 years (RH DeRijk and S Wüst, unpublished data; see Note added in proof). Moreover, patients carrying a specific mutation in the *FKBP5* (FK506 binding protein 5) gene, which encodes a protein that interacts with the glucocorticoid receptor, responded much faster to antidepressants than did a comparison group of people who did not carry this mutation.[18]

In animal studies, modulations of mineralocorticoid receptor and glucocorticoid receptor function can be achieved with pharmacological methods as well as those generated by gene transfer using a lentiviral approach locally in the brain in mouse models.[30] Mutant mice generated with receptor underexpression show increased stress-induced corticosterone secretion and a dexamethasone plus CRH test indicative of the expected corticosteroid resistance. The animals also show coping deficits.[31] This finding further supports the evidence that these receptors are critical components of the neuronal pathways involved in individuals susceptible to depressive illness.

Other lines of mutants carrying a point mutation in the glucocorticoid receptor that prevents dimerization and DNA binding display a deficit in memory storage, but do not show disturbances in emotional behavior and measures of anxiety.[32] Mice overexpressing the glucocorticoid receptor are resistant to these impairments and show an apparent healthier profile.[31] Although these models, based on generalized changes in glucocorticoid receptor expression, show promise and may allow reconstruction of depression symptoms, more-regionally localized disruptions in the glucocorticoid receptor have given conflicting results. For example, $GR^{CamII\ Cre}$ mutants (which lack glucocorticoid receptors in the limbic forebrain) already show increased anxiety and despair under basal conditions,[33] whereas the GR^{NesCre} knockouts (which have glucocorticoid receptors deleted from the whole brain) show the opposite features;[34] furthermore, overexpression of the glucocorticoid receptor in the limbic forebrain produces a state of emotional lability.[35]

Two further remarks can be made on the progress in these transgenic approaches. First, if the glucocorticoid receptor is modulated in

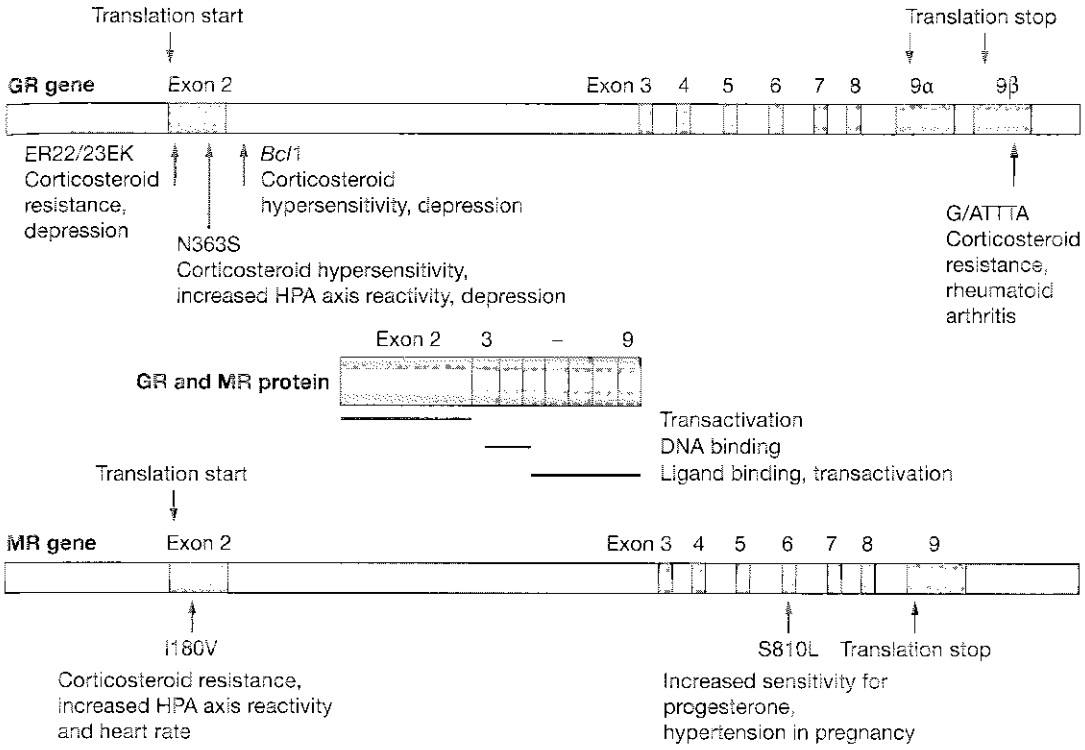

Figure 3 Variants in human MR and GR genes. The GR gene shows alternative splicing: either exon 9α or 9β can join exon 8, giving rise to GRα or GRβ. Indicated are functional single-nucleotide polymorphisms (SNPs) leading to amino acid changes in the GR (ER22/23EK, N363S) or in the MR (I180V, S810L),[88,89] and SNPs involved in messenger RNA stabilization (G/ATTTA for GR). The function of the GR *Bcl*1 (also termed *CCND1* [cyclin D1]) site is still unknown. The MR and GR protein can roughly be divided into three functional parts: a transcriptionally active domain, the DNA-binding domain and the ligand-binding domain, which also harbors a transcriptionally active domain. Specific effects and associations with pathology are indicated next to each SNP. Abbreviations: GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; MR, mineralocorticoid receptor.

function, an alternative interpretation could be that the observed effects are due to the mineralocorticoid receptor.[9,36] Second, cortisol signaling is subject to many more influences than those evoked by transgenic modulation of receptor number. This feature is illustrated by the SNP studies mentioned above. Cortisol resistance due to changes in sensitivity of receptors, chaperones and co-regulators can be expected to result in other phenotypes than those generated by upregulation or downregulation of the receptors.

Early-life experiences that can prime for depression

For a long time, early-life adversity has been known to increase vulnerability to stress-related psychiatric illness because it permanently alters HPA activity.[7,37,38] Progress in understanding how these persistent early-life effects occur is based on the pioneering studies of Seymour Levine.[39] He discovered that rats that are briefly separated from the dam as pups display in adulthood reduced emotional and neuroendocrine reactivity to common stressors. These lasting effects correlated with the extent of maternal care the pups had received on their return to the mother. Furthermore, in other experiments, offspring from mothers showing endogenous high degrees of licking and grooming behaviors had attenuated stress-system activity, improved cognitive performance in a spatial learning test and reduced anxiety-like behavior in adulthood compared with offspring that had received relatively little care.[40] If rat pups received little maternal care, a high level of stress responsiveness was observed in adulthood, but this outcome could be pre-empted by cross fostering the pups with mothers that performed a lot of licking and grooming.

Extended separation of mother and pup is a commonly used laboratory model for neglect.

In our experiments, pups exposed to 24 h of maternal separation at postnatal day 3 produced as adults enhanced corticosterone responses to a common stressor, and their cognitive performance was impaired.[41] The immediate effects of maternal deprivation could be obliterated if maternal behavior was mimicked by feeding and stroking the pups.[42] Prenatal adversity due to stress or dexamethasone treatment during pregnancy can also cause lasting changes in rodents.[43] Similar programming events might happen in nonhuman primates and humans.[44] A recent study in primates actually suggests that maternal care or the early experience of stressful events can determine the ability to cope with stress in later life (the inoculation hypothesis).[45]

These very challenging studies have shown that early-life experiences, probably through epigenetic changes,[46] can dramatically alter the genetically predisposed phenotype. Likewise, susceptibility pathways matured through adverse gene–environment interactions can still be modulated in later life. Even if the outcome in later life is an increased responsiveness and susceptibility to stressors, the risk of disease thus depends on the context in which the later-life stressful events are experienced.

The stress trigger

The ideal animal model to test the 'three hit' theory of disease should have susceptibility pathways matured by a history of adverse early-life experiences against a predisposing genetic background. In animal studies, however, 'chronic stress' models do not generally take into account genetic predisposition plus early adversity; the models are based on the daily experience of randomized unexpected stressors or psychosocial defeat, irrespective of early-life history. After long-term exposure to these stressors the animals usually show a hyperactive HPA axis and an apparent resistance to glucocorticoid feedback. Aminergic brain systems are also profoundly affected by chronic stress and high glucocorticoids. Although glucocorticoid synthesis and release are enhanced, at the target neuron level the postsynaptic responses are modulated. For instance, responses mediated by the 5-hydroxytryptamine 1A receptor are attenuated by chronic corticosteroid elevation, producing depression-like symptoms.[12,47] These stress-induced monoaminergic adaptations thus form a basis for the mechanism of action of antidepressants.

Fear-motivated behavior and cognitive impairment induced by chronic stress correlate in the hippocampus and amygdala with substantial structural changes, albeit with striking regional differences. The hippocampal CA3 region and areas of the prefrontal cortex show signs of atrophy mediated by glutamate and cell-adhesion molecules,[48,49] whereas the opposite effect, hypertrophy, is reported for the basolateral amygdala.[50] In the subgranular zone of the hippocampal dentate gyrus, neurogenesis is suppressed after chronic stress. These changes, which are induced by chronic stress, are mimicked with continuous exposure to high levels of glucocorticoids and are aggravated under conditions of diabetes, ischemia and epileptic seizures.[51,52]

Interestingly, inescapable shocks administered to rats' feet were associated with increased corticosterone levels and suppressed neurogenesis, but this stress effect was abrogated if the rats were socially housed.[53] Exercise improved neurogenesis even though corticosterone levels were also increased, but adverse conditions such as social isolation abolished the positive effects of exercise on neurogenesis.[54]

All conditions—positive experiences obtained through exercise or negative experiences obtained through foot shocks or defeat—elevated corticosterone levels, but it is the psychosocial context and the ability to cope that determines the phenotypic outcome. Accordingly, some unknown factor that is produced under the influence of 'context' is capable of changing the action of corticosterone from protective into harmful. Yet, the changes appear mostly reversible, and one could argue that extensive stress-induced remodeling occurring in the hippocampus, prefrontal cortex and amygdala is adaptive. Though adaptive, the potential for damage to result might be increased, as indicated by the reduced synthesis of cell-survival molecules under chronic stress.[55]

The remodeling and atrophy seen in the hippocampus has led to speculation about why the hippocampal volume is reduced in depression,[56] although no apparent neuronal damage was observed.[57] Hippocampal size has, however, been found to be genetically determined. The jury is, therefore, still out on the question of whether a small hippocampus is actually a risk factor for stress-related disease or is in fact an adaptation to adverse overexposure to stress hormones.[58]

CURRENT THERAPEUTIC APPROACHES THAT AFFECT THE HPA AXIS

Several novel approaches to developing antidepressant drugs have been explored, including neurokinins, endocannabinoids, neuropeptides and neurotrophic growth factors. Although some of these approaches are empirical, other strategies are based on a conceptual framework. The latter include the CRH or vasopressin antagonists aimed at attenuating hyperactivity of the HPA axis and ameliorating depressive symptoms. Approaches limiting overexposure to endogenous cortisol have also been used.[4,59,60]

The cortisol-targeting approach focused on cortisol synthesis inhibitors, glucocorticoid receptor antagonists or, paradoxically, glucocorticoid receptor agonists. Beneficial treatments were with metyrapone and ketoconazole, agents that diminish adrenocortical output.[61] Metyrapone was also effective as an adjunct to the effects of classical antidepressant therapy.[62] By contrast, a remarkable improvement was also observed with use of synthetic glucocorticoid agonists (e.g. dexamethasone, 3–8 mg daily).[63,64] An explanation for the antidepressant effect of dexamethasone could be the blockade of the HPA axis and hence depletion of endogenous glucocorticoid cortisol from the brain. When present at low concentrations, dexamethasone penetrates the blood–brain barrier poorly because of the presence of P-glycoprotein and does not substitute for corticosteroid depletion, hence producing the desired hypocorticoid state in the brain (Figure 2).[23]

Short-term use of the glucocorticoid receptor antagonist mifepristone (RU 486) gave positive results[60,65,66] and appeared capable of re-regulating the HPA axis.[67] The application of this antagonist of both progesterone and glucocorticoid receptors is most effective in patients with overt hypercortisolemia—that is, in treating psychotic symptoms in patients with Cushing's syndrome.[16] In an ongoing, phase III study, mifepristone is being tested for efficacy in psychotic depression characterized by hypercortisolemia that is resistant to antipsychotic and antidepressant therapy.[65] The drug has a remarkably fast effect and efficacy, but high doses are needed because of its rapid clearance and poor brain penetration. A 7-day regimen of 600 mg daily was thus needed, but no major side effects were noted.[65] Both in clinical[15,68] and in animal[69,70] studies mifepristone improved cognitive performance and reinstated the circadian corticosteroid pattern, suggesting recovery of the circadian and ultradian timing system linked to HPA activity.

Treatment with glucocorticoid-receptor antagonists might imply that the beneficial effects could be achieved by recovery of an imbalance between the mineralocorticoid receptor and the glucocorticoid receptor. Indeed, the clinical relevance of mineralocorticoid receptor function during depression was emphasized when spironolactone, a mineralocorticoid receptor antagonist, worsened the clinical outcome when administered in conjunction with antidepressant treatment.[59]

CONCLUSIONS

We have addressed here the question of the possible causative role of cortisol in depression and, accordingly, whether alterations in cortisol signaling offer potential treatment options. The antiglucocorticoid treatment of psychosis and of the cognitive abnormalities accompanying the illness is indeed a promising option.[67] Pathways responsive to the glucocorticoid receptor in specific limbic–cortical areas have been identified as pathophysiological candidates and provide an opportunity to target recovery from the proposed imbalance in the actions mediated by the mineralocorticoid receptor and the glucocorticoid receptor. Correction of the receptor balance is predicted to attenuate the susceptibility of 'depression' pathways and to improve resilience. The following new insights into the action of cortisol could further reinforce the treatment options for complex mood disorders such as depression.

First, if treatment requires correction of aberrant cortisol action, several factors should be taken into account to reinstate the desired resilience. These factors include simulation of the circadian and ultradian secretion patterns of the hormone[71] and understanding the precise timing of the cortisol regime in relation to the psychological context. Time and context are important because cortisol can facilitate the extinction of behavior that is no longer of relevance and thus allow consolidation and retrieval of relevant novel information.[24,26,72] This reasoning calls for an approach where the psychological context is created that allows cortisol to promote the storage of corrective experiences and to suppress retrieval of unwanted memories. The success of this approach has become apparent in human studies in which cortisol reduced phobic fear and symptoms of post-traumatic stress disorder.[73,74] This latter disorder is thought to be related to

inadequate amounts of cortisol,[75] and nothing precludes a similar rationale being true for using antiglucocorticoids to treat pathologies associated with excess cortisol levels.

Second, much progress has been made in understanding the action of cortisol through modulation of gene transcription. Microarray studies have identified waves of genes responsive to corticosteroids.[76] Reduced expression levels that can result from transrepression may limit the overshoot of stress reactions, and the reversal of this by transactivation underlie the recovery of functions such as those mediated by metabolic enzymes.[77] Studies have uncovered fast, nongenomic actions of cortisol involving the mineralocorticoid receptor in limbic brain structures that participate in appraisal, vigilance and (violent) reactivity,[25,26,78] and glucocorticoid-receptor-like actions in the neuroendocrine hypothalamus.[27,77] At least in the hippocampus, the classic mineralocorticoid receptor mediates this rapid steroid effect on excitatory transmission,[26] but endocannabinoids, nitric oxide or mitogen-activated protein kinase pathways[27,79] also seem to be involved. New compounds are, therefore, needed that can discriminate between the various temporal and mechanistic phases in (non)genomic cortisol actions.

Third, as a more remote strategy, genetic and early-life factors affecting maturation of susceptibility pathways might also provide novel targets. Questions to be resolved concern the identification of these neural susceptibility pathways and the chemical identity of the factors that converge to endow corticosteroids with either a harmful or a protective signal.

Lastly, this article was written with the perception that a new era has arrived in which depressed patients will increasingly be examined with functional and genetic tests to obtain a diagnostic 'fingerprint'. Such information from phenotyping and SNP maps might allow us to link disturbances in specific psychic domains with biological substrates. The actions of cortisol in the brain that are linked to depression and psychosis may be considered a milestone to reach these ambitious goals.

Note added in proof Since the submission of this paper, the efficacy of the glucocorticoid receptor antagonist mifepristone in the treatment of psychotic depression has been questioned.[80] The concerns raised have been addressed in the reply by Keller and Schatzberg.[81] In light of this discussion, the antagonist is well known to alleviate psychotic symptoms in patients with Cushing's disease.[16,82] In the context of high circulating cortisol levels, therefore, the antipsychotic efficacy of mifepristone has been established. In a large, double-blind study positive results were reported, with mifepristone being associated with a rapid and sustained reduction in the psychotic symptoms of patients who have psychotic depression;[83] however, the first phase III clinical trials using the drug as add-on therapy with classic antidepressants and antipsychotics have been inconclusive.[84] How the antagonist achieves its beneficial effects in the treatment of psychoses is not known. Interesting new leads are arising from animal studies showing that mifepristone is capable of rapidly reversing the effects of a high corticosteroid environment on brain functions, as was observed for robust readout parameters of neurogenesis in the rat hippocampus.[85–87] Finally, the work cited in the text as 'RH DeRijk and S Wüst, unpublished data' has now been published.[88,89] It remains to be established to what extent the recently discovered functional corticosteroid receptor polymorphisms contribute to the efficacy of mifepristone.[19,28,29,88,89]

KEY POINTS

- Corticosteroid action in the brain is mediated by the high-affinity mineralocorticoid receptors, which protect neurons in stress, and lower-affinity glucocorticoid receptors, which promote recovery of neurons
- Corticosteroids are generally protective but become harmful in excessive or inadequate concentrations, a change that is thought to depend on the context in which the mineralocorticoid and glucocorticoid receptors operate in pathways susceptible to stress in the brain
- The maturation of susceptibility pathways depends on genetic factors and can be shaped by epigenetic processes that depend on the maternal environment
- Targets for intervention in phenotypes vulnerable to stress-related psychiatric disorders are found in corticosteroid-responsive susceptibility pathways in the brain; potential drugs include specific ligands for the receptors, which in future may discriminate between different modes of action—at the level of membranes, gene transactivation and transrepression

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