

STRESS AND THE BRAIN: FROM ADAPTATION TO DISEASE

*E. Ron de Kloet**, *Marian Joëls[‡]* and *Florian Holsboer[§]*

Abstract | In response to stress, the brain activates several neuropeptide-secreting systems. This eventually leads to the release of adrenal corticosteroid hormones, which subsequently feed back on the brain and bind to two types of nuclear receptor that act as transcriptional regulators. By targeting many genes, corticosteroids function in a binary fashion, and serve as a master switch in the control of neuronal and network responses that underlie behavioural adaptation. In genetically predisposed individuals, an imbalance in this binary control mechanism can introduce a bias towards stress-related brain disease after adverse experiences. New candidate susceptibility genes that serve as markers for the prediction of vulnerable phenotypes are now being identified.

HYPERCORTISOLAEMIA
Excess levels of circulating cortisol.

**Department of Medical Pharmacology, Leiden Amsterdam Center for Drug Research and Leiden University Medical Center, Gorlaeus Laboratories, Leiden University, PO Box 9502, 2300 RA Leiden, The Netherlands.*

[‡]*Swammerdam Institute for Life Sciences, University of Amsterdam, Kruislaan 320, 1098 SM Amsterdam, The Netherlands.*

[§]*Max Planck Institute of Psychiatry, Kraepelinstrasse 2–10, 80804 Munich, Germany.*

Correspondence to E.R.d.K.
e-mail: e.kloet@lacdr.leidenuniv.nl

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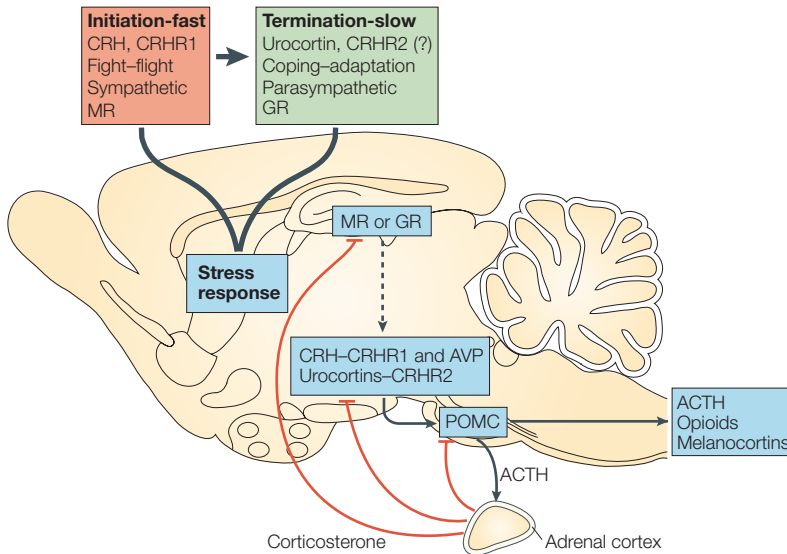
All living organisms strive towards a dynamic equilibrium, which is called homeostasis. In the classical stress concept, this equilibrium is threatened by certain physical and psychological events that are known as ‘stressors’^{1–8}. As a result, behaviour is directed towards appraising the destabilizing potential of the stressor. If the event fails to match some cognitive representation based on previous subjective experience, there is a surge in arousal, alertness, vigilance, focused attention and cognitive processing. The interface between the incoming sensory information and the appraisal process is formed by limbic brain structures, which include the hippocampus, amygdala and prefrontal cortex.

Stressors also trigger physiological and behavioural responses that are aimed at reinstating homeostasis. This ‘stress response’ is reflected in the rapid activation of the sympathetic nervous system, which leads to the release of noradrenaline from widely distributed synapses and adrenaline from the adrenal medulla. Blood concentrations of adrenal glucocorticoids also rise to peak levels after 15–30 min and then decline slowly to pre-stress levels 60–90 min later. As well as homeostatic disturbance, purely psychological processes can determine the magnitude of the stress response. In the psychological realm, the response determinants include the ability to predict

upcoming events and to exert control over the situation. Effective coping implies that the stress response is activated rapidly when it is needed and is efficiently terminated afterwards. The processes that underlie the stress response have been collectively termed ‘allostasis’⁸. In the first part of this review, we highlight the adaptive stress-related processes that take place in limbic brain regions.

If the stress response is inadequate or excessive and prolonged, the cost of reinstating homeostasis might become too high, which is a condition that is termed allostatic load⁸. In the second part of this review, we discuss how such an inappropriate stress response in animals produces a vulnerable phenotype and acts as a trigger for mechanisms that leave genetically predisposed individuals at an increased risk of (mental) illness. In the third and final part of this review, we address how, in genetically predisposed humans, these situations might evolve into enhanced sympathetic nervous system activity combined with HYPERCORTISOLAEMIA, as seen in depression^{9,10}, or with hypocortisolaemia, as found with POST-TRAUMATIC STRESS DISORDER (PTSD)¹¹. We also address why maladaptive changes produce stress-related brain disorders in some individuals, whereas others remain in excellent health under similar adverse conditions.

Box 1 | The brain as an inducer and target of corticosteroids



The stress system has two modes of operation. The fast mode involves the corticotropin-releasing hormone (CRH)-driven sympathetic and behavioural ‘fight-flight’ response, which is mediated by the CRH1 receptor (CRHR1). CRHR1 also activates the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis involves CRH and vasopressin (AVP), which are produced in the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN); these neurons secrete the peptides into the portal vessel system to activate the synthesis of pro-opiomelanocortin (POMC) in the anterior pituitary, which is processed to corticotropin (ACTH), opioid and melanocortin peptides, among others. ACTH stimulates the adrenal cortex to secrete cortisol (in humans) and corticosterone (in humans, rats and mice). Several afferent pathways activate the CRH neurons in the PVN; these include limbic pathways that are activated by psychological stressors, and ascending brain-stem pathways that convey visceral and sensory stimuli.

The other slower mode that promotes adaptation and recovery is governed by the recently discovered urocortins II and III, which act through the CRHR2 system^{163,164}. The CRHR1 and CRHR2 systems have a partly overlapping distribution in the brain, which matches their CRH and urocortin terminal fields, respectively. Intracerebroventricular administration of CRH mimics the initial behavioural, autonomic and neuroendocrine stress response, and is anxiogenic, whereas urocortins seem to have anxiolytic properties¹⁶⁵.

Corticosteroids operate in both stress-system modes through mineralocorticoid and glucocorticoid receptors (MRs and GRs, respectively), which are co-expressed abundantly in the neurons of limbic structures¹⁷. MR is implicated in the appraisal process and the onset of the stress response. GR, which is only activated by large amounts of corticosteroid, terminates the stress reactions, mobilizes the energy resources required for this purpose and facilitates recovery. GR promotes memory storage in preparation for future events. Therefore, the two stress systems form interacting signalling networks that underlie adaptive processes ranging from the appraisal of an unfamiliar stimulus to memory storage and retrieval. They also participate in various aspects of the control of energy metabolism, from appetite and macronutrient choice to energy disposition and storage.

Stress action in the brain: towards adaptation

Binary action of hormonal systems. When a situation is perceived as stressful, the brain activates many neuronal circuits to adapt to the demand. Two neuropeptides, corticotropin-releasing hormone (CRH) and vasopressin (AVP), are essential for coordinating the behavioural and metabolic responses to stress. The hypothalamic release of CRH and vasopressin govern

the HYPOTHALAMIC–PITUITARY–ADRENOCORTICAL (HPA) AXIS, the activity of which is reflected in blood concentrations of corticosteroid hormones (BOX 1).

Corticosteroids reach every organ by way of the circulation, which allows the coordination of brain and body functions that are geared towards coping with stress, recovery and adaptation. To exert this crucial life-sustaining function, corticosteroids mobilize substrates for energy metabolism and dampen primary stress and immune and inflammatory reactions to prevent them from overshooting⁶ (metaphorically, “glucocorticoids contain the water damage caused by the fire brigade⁷”). The underlying mechanism involves an integrated response, which starts with rapid hormone-induced changes in receptor conformation that lead to slower modulations of gene transcription (BOX 2).

The receptor system that mediates the slow genomic actions of corticosteroids has several remarkable features. First, it consists of two related receptor molecules, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which bind the same hormone (primarily cortisol in humans and corticosterone in rodents) in the brain, albeit with a tenfold difference in affinity^{12,13}. MR affinity seems sufficiently high to maintain receptor activation throughout 1-h intervals between hormone secretory bursts of 20-min duration. By contrast, the lower affinity GR seems to respond largely in phase with the ULTRADIAN RHYTHM. This receptor becomes progressively activated during stress- and circadian-induced increases in the frequency and amplitude of corticosteroid secretory bursts^{14,15}.

Second, GR distribution is ubiquitous, although uneven, in neurons and glial cells. GR density is highest in the parvocellular paraventricular nucleus (PVN) of the HPA axis, in neurons of ascending AMINERGIC PATHWAYS and in limbic neurons that modulate PVN function trans-synaptically through pathways that impinge on an inhibitory hypothalamic GABA (γ-aminobutyric acid) network that surrounds the PVN^{16,17}. Limbic neurons also express MRs abundantly. Considerable MR and GR co-expression is found in hippocampal pyramidal cell fields (except the adult CA3, which shows minimal GR expression) as well as the dentate gyrus, the amygdaloid and lateral septal nuclei, and some cortical areas. MR and GR co-localization is found in the hippocampus of almost all species¹⁸.

Third, corticosteroids seem to operate in a binary fashion to target gene networks that underlie the acute and late-recovery phases of the adaptive stress reaction (FIG. 1). The formation of MR and GR homodimers and heterodimers, as well as monomers, allows receptor responsiveness over a wide concentration range^{19,20}. In the recovery phase, GR monomers can interfere with transcription factors and repress stress-induced responses, such as peptide synthesis (including that of CRH and vasopressin), and thereby terminate ongoing stress reactions. This suppression is not uniform, as GR dimers can also activate extrahypothalamic (amygdaloid) CRH and ascending aminergic systems, and metabolic enzymes. Corticosteroid receptor function, neurotransmitters and neuropeptides are intrinsically

POST-TRAUMATIC STRESS DISORDER (PTSD). The symptoms of PTSD consist of re-experiencing an extreme stressor or traumatic event, avoidance of reminders of the event and hyperarousal.

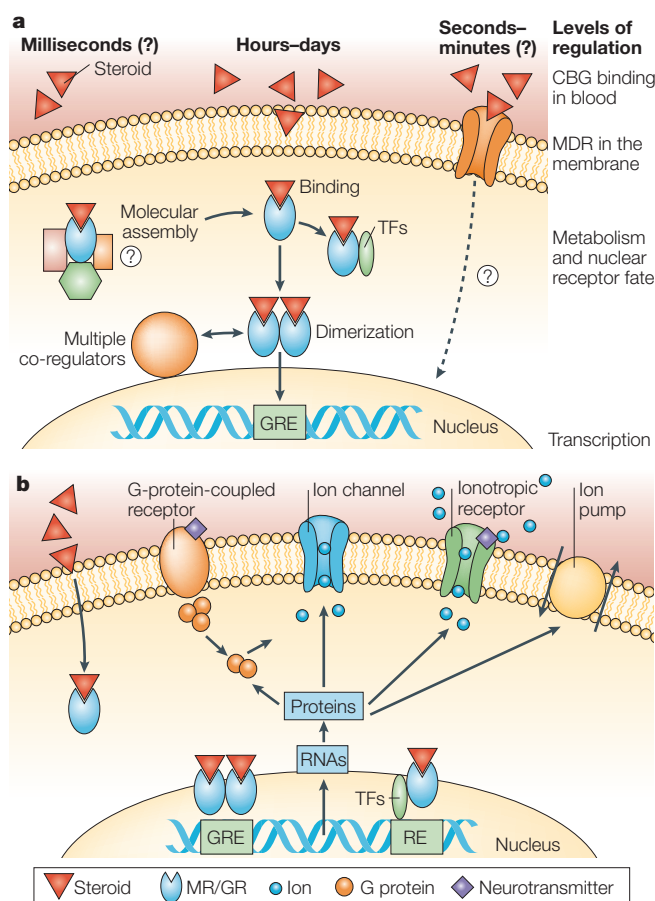
Box 2 | Diversity of mineralocorticoid and glucocorticoid receptor signalling in limbic neurons

On binding corticosterone, the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) multimeric protein complex dissociates (panel a). For the effects on gene expression, MRs and GRs, functioning either as homodimers or heterodimers, interact at a glucocorticoid-response element (GRE) and recruit co-repressors or co-activators, whereas GR monomers interact with stress-induced transcription factors (TFs) or other proteins to dampen their transcriptional activity¹⁶⁶. The rapid responses, which involve steroid-induced conformational changes and reaggregation with other proteins (such as heat-shock proteins (HSPs)), and a putative membrane steroid receptor, remain poorly understood.

Signalling can be regulated at several levels. First, through the corticosteroid-binding globulin (CBG) in blood, which is important for the availability of corticosterone. Second, through multidrug resistance (MDR) P glycoprotein in the blood-brain barrier (BBB), which hampers the penetration of synthetic glucocorticoids and some naturally occurring glucocorticoids into the brain¹³⁵. Third, through the multimeric receptor-protein complex. On binding corticosterone, factors such as HSPs dissociate, changing the conformation of the receptor. Fourth, through steroid metabolism¹⁵². Unlike MRs

in typical aldosterone targets, such as the kidney, sweat glands and brain circumventricular organs, MRs in most parts of the brain lack specificity for aldosterone, which circulates at a 100-fold lower concentration than corticosterone. The latter aldosterone specificity is achieved by an oxidase that converts corticosterone into its inactive 11-dehydrometabolite before receptor binding. In the brain, the isoform that catalyses this reaction is restricted to regions that are involved in the regulation of salt appetite and volume. Another isoform that promotes the reverse reaction to regenerate bioactive cortisol is active in the liver and limbic brain. Steroids can also be converted to neurosteroids that directly interact with and modulate membrane receptors, such as the GABA (γ -aminobutyric acid) receptor. Fifth, through interaction of GR with transcription factors, such as nuclear factor- κ B (NF- κ B) and activator protein 1 (AP1). Sixth, through the interactions of MR and GR with co-regulators; the recruitment of co-repressors and co-activators induces the repression and transactivation of gene expression, respectively⁹⁰.

The effects of steroids on membrane properties are shown in panel b. On binding to corticosterone, MR and GR can regulate the transcription of genes that are involved in controlling the properties of G protein-coupled receptors, ion channels, ionotropic receptors and ion pumps. This leads to changes in the conductance of the plasma membrane. These steroid actions are conditional, slow in onset and long lasting. RE, response element.



intertwined²¹. Limbic network properties are altered such that experiences are remembered and stress responsiveness is maintained for future events.

Molecular and cellular changes. As corticosteroid receptors function as transcriptional regulators, the first step that leads to their ultimate effect on adaptive behaviour involves the altered expression of responsive genes. Recently, large-scale gene-expression-profiling methods, such as SERIAL ANALYSIS OF GENE EXPRESSION (SAGE) and DNA MICROARRAYS, have been applied to identify these genes, using an experimental

design that mimics differential MR and GR occupation. In the hippocampus, the activation of MRs or GRs led to the altered expression of 70–100 genes, of which roughly 50% were upregulated. One-third of the genes were responsive to both receptor types²². These findings indicated that corticosteroids coordinate the expression of high- and medium-abundant genes that underlie aspects of cell metabolism, structure and synaptic transmission. Some of the genes included known GR targets, such as enzymes and receptors for biogenic amines and neuropeptides²³, growth factors^{24,25} and cell-adhesion factors²⁶.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

(HPA axis). The HPA axis is the endocrine core of the stress system, which involves hypothalamic corticotropin-releasing hormone, pituitary corticotropin and adrenal cortisol.

ULTRADIAN RHYTHM

The regular recurrence of cycles of less than 24 h from one stated point to another.

AMINERGIC PATHWAYS

Systems that involve serotonin or catecholamines.

SERIAL ANALYSIS OF GENE EXPRESSION

(SAGE). This method allows the analysis of overall gene-expression patterns. SAGE does not require a pre-existing clone, so it can be used to identify and quantify new as well as known genes.

DNA MICROARRAY

Technology that can simultaneously measure the expression patterns of thousands of genes on a single chip.

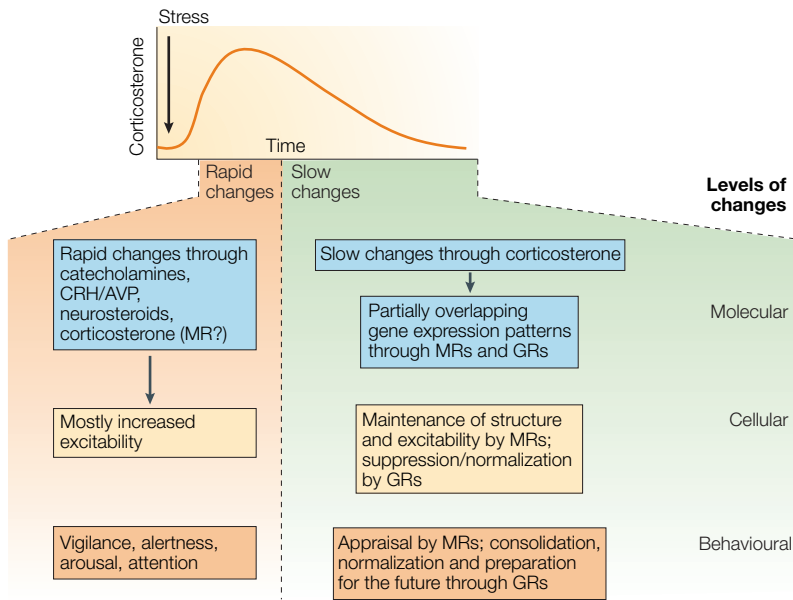


Figure 1 | Time course of cellular responses to stress hormones. Activation of the hypothalamic–pituitary–adrenocortical (HPA) axis by stress leads to a temporary rise in circulating corticosteroid levels, as exemplified by the changes in hormone levels over time shown in the graph (see also BOX 1). The hormone levels are usually normalized by 2 h after the onset of the stress. In the early phases of the stress response, when the corticosteroid levels rise, fast-acting agents (such as catecholamines, neuropeptides and possibly corticosterone itself) contribute to an adequate response to the stressor, which leads to enhanced vigilance, alertness, arousal and attention. Gradually, gene-mediated corticosteroid effects take over through the transcriptional regulation of specific sets of genes by the mineralocorticoid and glucocorticoid receptors (MRs and GRs, respectively). This affects cellular function in cells that carry these receptors, such as CA1 hippocampal cells. Typically, the dose-dependence curve of these cells for the hormone is U-shaped. The MR- and GR-mediated actions affect structural integrity and excitability, and proceed in a coordinated manner, which is linked in time to a particular stage of information processing. The MR is mostly responsible for the maintenance of the stress-related neural circuits, and is implicated in the appraisal of sensory information and its organization, whereas the GR is important for the normalization of homeostasis and the storage of information in preparation for future use. AVP, vasopressin; CRH, corticotropin-releasing hormone.

These observations underpin the relevance of corticosteroids as structural modulators in limbic areas. In the CA3 hippocampal area, a single stressor led to a delayed loss of apical dendrites but an enhanced basal dendritic tree²⁷. In the dentate gyrus, the maintenance of dendritic structure and size depends on MR occupation²⁸. The MR and GR were also found to be important with regard to neurogenesis in the dentate gyrus²⁹. The activation of MR is necessary to restrain proliferation, as well as apoptotic cell death, in this region^{30,31}. This involves the regulation of several pro- and anti-apoptotic genes³² after the activation of the corticosteroid receptors³³. Brief exposure to stress temporarily suppresses proliferation and increases cell death^{34–36}. The functional relevance of a brief arrest in cell proliferation after an acute stressor might be limited, as it pertains to an extremely small fraction of the overall population of dentate cells. However, it could become relevant if it reflects a more generalized structural reorganization.

Although large-scale expression profiling points to structural proteins as the endpoints of corticosteroid action, this approach is not yet informative about the

gene transcripts that underlie electrical and chemical communication, because their abundance is too low to be reliably detected. However, electrophysiological studies have clearly indicated that such molecules are prominent targets of stress hormones. Some common principles have become evident over the years with regard to the effects of stress hormones on the electrical properties of limbic cells³⁷ (FIG. 1). First, corticosteroid hormones, particularly when acting through GRs, usually have little effect on cellular properties under resting conditions and their effects only become evident when the cells are driven from their resting potential. In this manner, GR activation can reverse noradrenaline-induced excitation³⁸.

Second, corticosteroids are pleiotropic agents, as might be expected of hormones that regulate the transcription of several genes. The functions of the diverse proteins that are involved — for example, in voltage-gated ion-channel function or G-protein-coupled receptor signalling — are strongly affected by corticosterone and stress. The serotonin (5-hydroxytryptamine, or 5-HT) 5-HT_{1A} receptor has been particularly well studied in this regard^{39,40}. Inhibitory responses through this receptor were found to be weak under basal conditions, but increased markedly with GR activation. In the absence of corticosterone, responses were similar to those seen with the concurrent activation of the receptors, which yielded a U-shaped dose-dependency. This U-shape turned out to be a typical feature of most cellular properties that are affected by corticosteroids in the CA1 area³⁷.

Although they are pleiotropic in their effects, steroids do not change all cellular properties. For instance, L-type calcium-channel function is markedly affected^{41,42}, whereas the function of potassium and sodium channels seems to be less prominently altered. The effects of stress and corticosterone on ionotropic receptors are generally relatively rapid and independent of the slow gene-mediated pathways. This applies to the effects on glutamate release in the hippocampus⁴³ and also in the hypothalamus, which involve endocannabinoids⁴⁴. These rapid corticosteroid actions might form a bridge between the rapid effects that are mediated by catecholamines and CRH, and the delayed actions that are mediated by corticosterone through gene transcription. Stress also exerts relatively slow effects on AMPA (α -amino-3-hydroxy-5-methyl-4 isoxazole propionic acid) glutamate receptor (GluR1) subunit recruitment⁴⁵.

The two receptor systems also function in a binary fashion at the cellular level⁴. In general, the effects of MR activity on cellular communication maintain the excitability and stability of networks. Conversely, GR (in addition to MR) activation leads to delayed suppression or normalization of network activity (FIG. 1). By allowing more calcium influx into the cell on depolarization, GR activation might facilitate the retention of information. However, enhanced calcium influx could also prime limbic neurons for the detrimental effects that might develop when networks are sufficiently challenged by concurrent adverse situations, such as an ischaemic insult.

Networks and behaviour. Basal corticosteroid levels are associated with the effective induction of LONG-TERM POTENTIATION (LTP) in the hippocampus⁴⁶, which is currently the best-documented neuronal substrate for memory formation⁴⁷. By contrast, high levels of corticosterone, stress or exposure to a new environment have been consistently shown to impair subsequently induced LTP and to facilitate long-term depression^{48–50}. Little is known about the mechanism through which these stress-induced changes are accomplished, although NMDA (*N*-methyl-D-aspartate) receptors seem to be involved⁵¹. Clearly, GR- or stress-mediated changes in glutamate transmission and calcium influx affect the potential for synaptic plasticity, although not necessarily in the direction of impaired LTP. The crucial issue seems to be the timing of events. If stress hormones reach limbic areas, they might alter network function — through the rapid effects of CRH⁵², neurosteroids⁵³ or even corticosterone itself^{54,54} — so that subsequent patterned input that is unrelated to the stress (for example, electrical stimulation or a learning-induced situation) is less effective at strengthening the synapses⁵⁵. However, if stress hormones are released in conjunction with the learning situation, and cause hormone release and network activation to concur, they might prime synapses so that synaptic potentiation is facilitated.

Timing has not been investigated in great detail with regard to LTP, but it has been addressed in behavioural studies. MRs and GRs affect complex learning models, such as spatial orientation, in a coordinate manner. Intracerebroventricular administration of GR antagonists immediately after the learning phase in a water maze impaired retrieval measured 24 h later⁵⁶. The GR antagonist was not effective immediately before the retrieval test, which indicated that the antagonist interfered with consolidation rather than retrieval. GR^{dim/dim} mutant mice, which carry a point mutation that prevents GR dimerization and DNA binding, also showed impairments in memory storage⁵⁷. So, GR activation seems to be a prerequisite for the storage of relevant information for future use. Conversely, in a water maze, MR blockade did not interfere with the ability to locate the platform but did alter the search pattern, which indicated an adaptational role for MRs in the appraisal of environmental stimuli.

Whereas task-related elevations in corticosterone seem to be essential for consolidation^{56,58,59}, GR activation before retention seems to interfere with previously acquired information. For instance, stress before the retrieval test in a Morris maze reduced the swim time in the former platform quadrant⁶⁰. This could be interpreted as a retention deficit that was entirely owing to altered GR function, but could also be regarded as behavioural extinction through the active consolidation of new and more appropriate information⁶¹.

The involvement of specific brain regions and transmitter systems also determines the outcome of hormonal effects. For example, memories are longer lasting when a situation is arousing⁶². The

basolateral amygdaloid nucleus (BLA), CRH and noradrenaline seem to be crucial for this process⁵⁹. It has been shown that corticosteroid effects on the consolidation of memory in fear conditioning, the Morris water maze and object recognition require concomitant noradrenergic input. At the cellular and network levels, these processes are only just starting to be understood. For instance, GR-enhanced calcium influx⁶³ might promote synaptic potentiation in the BLA⁶⁴, as voltage-gated ion channels (in addition to NMDA receptors) have an important role in LTP in this region.

Stress-hormone effects in the BLA seem to be important for network changes in areas that are reciprocally connected with the amygdala, such as the hippocampus^{65,66} and the prefrontal cortex⁶⁷. The combined effects of stress hormones in all of these areas, which might be differentially involved depending on the type and severity of the stressor, determine the overall outcome. A potent modulator of the effect of the stressor seems to be the extent of behavioural control. A recent study indicated that stressor controllability inhibits the stress-induced activation of dorsal raphe serotonergic neurons through infralimbic and prelimbic ventral-medial prefrontal cortex input⁶⁸. This finding could explain how coordinated MR- and GR-mediated effects, depending on the context (controllability), might modulate the consequences of stress.

The vulnerable phenotype in animal models

Traumatic experiences in early life or acute and chronic stressors challenge the capacity of an individual to cope. If coping fails, various events occur that result in a long-lasting state of distress, which is reflected in aberrant HPA axis activity and altered limbic function.

The chronically stressed animal. Acute and traumatic inescapable stressors in adulthood can have lasting consequences on the brain and behaviour. Most 'chronic stress' models are based on exposure of an organism to several weeks of daily immobilization, a selection of randomized stressors twice daily or repetitive social stressors, such as daily exposure to a dominant male. Although these procedures do not have similar outcomes for all stress parameters, they cause severe deficits in hippocampus-related memory^{26,48}. In addition, chronically stressed animals show increased fear-motivated behaviour^{69,70}. The neural correlates of the behavioural deficits have been documented in the hippocampus, amygdala and prefrontal cortex, and include aspects of structural remodelling and cell proliferation, as well as changes in amine, neuropeptide and corticosteroid systems (FIG. 2).

One of the most consistent effects of chronic stress is a reduction in the branching and length of CA3 pyramidal apical dendrites, along with a decreased number of synaptic contacts^{71–73}. Similar reduced branching has been reported for the principal neurons in the prefrontal cortex⁷⁴. By contrast, repeated immobilization stress causes hypertrophy in the basolateral

LONG-TERM POTENTIATION

The prolonged strengthening of synaptic communication, which is induced by patterned input and is thought to be involved in learning and memory formation.

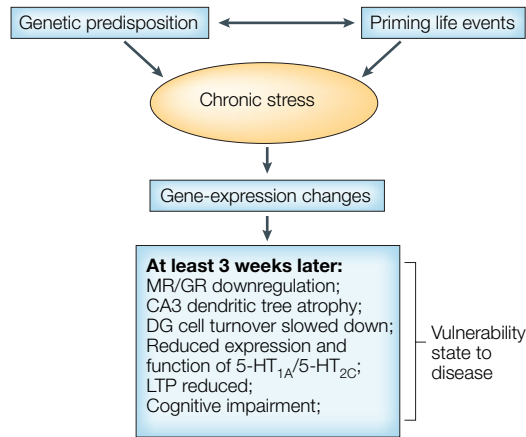


Figure 2 | Gene–environment interactions produce a vulnerable phenotype. Responses to several or long-lasting stressors in adulthood depend on genetic predisposition and are modulated by the history of the individual, particularly during early life. Genetic background might, to some extent, also predispose to early-life events and early-life history (such as maternal care) can, in turn, change the genetic profile through epigenetic pathways. All of these factors determine whether the organism is susceptible or resilient to severe stressors in adulthood. Vulnerable individuals might display changes in corticosteroid receptor expression, atrophy of hippocampal cells, reduced neurogenesis, altered monoaminergic signalling, reduced synaptic plasticity and impaired learning ability, which can, ultimately, lead to a diseased state. DG, dentate gyrus; GR, glucocorticoid receptor; LTP, long-term potentiation; MR, mineralocorticoid receptor; 5HT_{1A}/5-HT_{2C}, serotonin (5-hydroxytryptamine, or 5-HT) receptors.

amygdala⁷⁵. Glutamate, which is the main transmitter for all of these neurons, might be causative for the structural alterations, as NMDA-receptor blockers prevented dendritic atrophy in the hippocampus after chronic stress. In addition, vesicles in the glutamatergic mossy fibre terminals that synapsed onto CA3 neurons were redistributed⁷⁶, which indicates stronger and perhaps excitotoxic input. In agreement with this idea, chronic stress specifically enhanced NMDA-receptor-mediated responses in CA3 neurons⁷⁷, whereas in the dentate gyrus, AMPA receptor-mediated responses were increased⁷⁸. Nevertheless, LTP was impaired in all hippocampal subareas⁷⁹. As detailed time courses of both physiological and structural changes after chronic stress are not yet available, it remains possible that overexposure to glucocorticoids, which target genes that encode structural proteins, primarily change dendritic morphology, which, in turn, changes the electrotonic length of the tree and, secondarily, also changes the glutamate-induced voltage shifts in the soma.

Another structure-related change involves the proliferation of progenitor cells in the dentate subgranular zone. Whereas acute stress only temporarily suppressed proliferation and increased apoptotic cell death, chronic exposure to elevated corticosteroid levels caused a longer-lasting reduction in proliferation and survival, although a partial reversal was seen after

several weeks of recovery^{36,80–82}. Apoptosis was also reduced, which pointed to a general slowing down of the cell cycle. With prolonged exposure to stressors, this might have considerable consequences for the nature and age of the neurons in the dentate gyrus and, therefore, for cognitive processes, such as impaired learning, in situations in which the dentate gyrus is important. Interestingly, stress-induced suppression of proliferation was prevented by the antidepressant tianeptine^{81,83} and by CRH or vasopressin antagonists⁸⁴. This is probably owing to the intrinsic effects of antidepressants on cell proliferation, as chronic treatment with imipramine and fluoxetine increased neurogenesis. The effect of the selective serotonin reuptake inhibitor (SSRI) fluoxetine was abolished in a 5-HT_{1A}-receptor knockout mouse⁸⁵. When neurogenesis was blocked by X-ray exposure, the behavioural effects of the antidepressants were eliminated. This finding led to the proposal that antidepressants might exert their actions by promoting neurogenesis, although caution should be exercised when extrapolating these findings to the pathogenesis of depression.

At present, it is unclear whether the effects of lasting or repeated stressors on hippocampal remodelling proceed directly through MR- and GR-mediated actions on structural and cell-cycle genes in neurons⁸⁶, as indicated by the identification of responsive target genes. In general, MRs and GRs respond to acute challenges, but seem to adapt to chronic treatments^{87,88}. However, the corticosteroid signalling cascade is complex and involves numerous chaperones, accessory proteins, co-regulators and interacting transcription factors (BOX 2) that permit differentiation between GR- and MR-mediated actions^{89,90}. This might be altered after long-lasting stress.

In addition to the corticosteroid receptors, other mediators, such as growth factors or the central monoaminergic system, have also been implicated in altered brain function after chronic stress or glucocorticoid exposure. For instance, although acute stressors stimulate the activity of monoaminergic systems in the brain — an effect that is mediated, in part, by glucocorticoids — sustained exposure to stress or glucocorticoids attenuates these systems. This is exemplified by attenuated 5-HT_{1A} receptor function in the CA1 region, generally downregulated 5-HT_{1A} receptor expression in the dentate gyrus, increased 5-HT_{2C} receptor expression, and decreased 5-HT turnover and release^{91–93}. During chronic stress, noradrenaline and CRH mutually enhance the activity of one another in the amygdala–locus coeruleus circuitry⁹⁴. Chronic stress, particularly when coping is impossible, attenuates the rewarding value of stimulating the mesocortical dopaminergic system and inhibits dopamine release in various terminal areas, including the hypothalamus⁹⁵.

The monoaminergic system and the corticosteroid receptors also interact to establish changes in the brain. This probably occurs predominantly through brain MRs, as GRs are relatively resistant to the effects of chronic stress^{87,88}. Moreover, the manipulation of

5-HT, noradrenergic and peptidergic inputs to the hippocampus enhances the expression of the MR in particular^{21,96–100}. This might have profound implications for the structural integrity of the dentate gyrus, as several approaches have identified the MR as a crucial factor in the control of dentate gyrus neurogenesis and cell death^{30–34,101}. Therefore, the induction of MR by antidepressants might mediate the recently reported drug effects on neurogenesis⁸⁵.

Inter-individual differences. Stress reactivity in adulthood is modulated by genetic background as well as early experience (FIG. 2). Genetic background can modulate the response to adversity in early life as well as in adulthood. Numerous rat and mouse lines have been bred for behavioural traits that resemble the most prevalent symptoms of affective disorders. This includes genetic selection for anxiety and aggression traits, and for dysregulations in HPA and biogenic amine systems^{102–110}. By selectively and bidirectionally breeding Wistar rats for either high-anxiety-related behaviour (HAB) or low-anxiety-related behaviour (LAB), an animal model was generated that showed the same normalization in neuroendocrine tests as that seen in patients with depression when treated with antidepressants^{104,105}. A HAB-specific allele of the vasopressin gene promoter was shown to contain a mutation that disrupts cognate binding of the transcriptional repressor CARG binding factor A, which consequently results in vasopressin overexpression in this particular rat line¹⁰⁶.

Another model involves wild house mice that are selected for either long or short latency before attacking an intruder in their home territory¹⁰⁷. These two groups represent the extremes of the coping mechanisms that co-exist in any population¹⁰⁸. The short attack-latency (SAL) mice are aggressive and display an innate active fight-flight coping mechanism towards environmental challenges; they have high stress-induced sympathetic activity and low adrenocortical output. By contrast, the long attack-latency (LAL) mice are non-aggressive, parasympathetically dominated and have a cautious passive coping mechanism that is characterized by freezing. In response to stress, LAL mice have much higher CRH mRNA expression, HPA activity and corticosterone output¹⁰⁹. Repeated sensory, but not physical, contact showed a change in the passive LAL mice towards a 'depression-like' neuroendocrine phenotype¹¹⁰.

These are just a few examples of the many rodent lines that have been selected for genetic traits that are related to stress. One caveat of this approach is that with selection for anxiety, aggression or other coping related traits, a host of other changes co-segregate and, in most cases, result in altered MR and GR expression. The interrelationships and causality of the various changes are often obscure, particularly in inbred animals, which limits the relevance of data from such lines with regard to complex human diseases.

In addition to genetic background, early experience predicts health outcome, as has been reported in animal models of prenatal materno-fetal¹¹¹ and postnatal mother-offspring interactions¹¹². In the pioneering studies of Seymour Levine^{113,114}, rat pups that were briefly separated from the dam showed reduced emotional and neuroendocrine reactivity to common stressors in adulthood. These effects persisted into old age¹¹⁵ and seemed to be caused by the enhanced maternal care that the pups received on their return, which included maternal licking, grooming and arched-back nursing. The offspring of high licking and grooming mothers showed attenuated stress-system activity, improved cognitive performance in a spatial-learning test and reduced anxiety-like behaviour in adulthood^{112,116}. A recent study proposed that the programming effect that is exerted by maternal behaviour is associated with a single gene: the *GR* gene. The offspring of 'caring' mothers had higher hippocampal *GR* expression, owing to demethylation of a cysteine residue at the 5' NGF1A binding region in the exon 1, promoter¹¹⁷.

By contrast, repeated separations daily for 3 h produced a phenotype later in life that was characterized by enhanced emotional and HPA responsiveness to brief stressors¹¹⁸. Moreover, CRH mRNA expression was enhanced in the central amygdala and PVN. The GR mRNA was decreased, particularly in cortical areas. Rats that were subjected to a single 24 h maternal deprivation were also used as a laboratory model of neglect. This procedure caused lifelong changes in stress responsiveness and cognitive performance¹¹⁹. During midlife, 5-HT_{1A}-receptor-mediated responses in the hippocampus were attenuated¹²⁰, and all rats showed hyper-responsiveness to an unfamiliar stressor and impairment of spatial learning. However, during the ageing process, a dichotomy developed: some deprived animals maintained excellent cognitive performance into old age, whereas performance in others deteriorated, which indicates that early experience might amplify individual trait differences¹¹⁹.

These studies show that HPA responsiveness and CRH expression are permanently altered in rodents as a result of early life experience. Importantly, in lines that have been selected for a genetic trait, such as a high or low propensity to develop learned-helplessness behaviour¹⁰² or responsiveness to apomorphin¹⁰³, the same early life adversity can have different consequences in individual animals for stress reactivity later in life. Early adversity, in combination with the genetic background, seems to sensitize certain circuits in the brain to an acute stressor. Consequently, the stress axis is persistently altered in reactivity, as reflected in an altered MR/GR balance. Several lines of evidence indicate that the same might happen in both non-human primates and humans^{121,122}.

Stress as a risk factor for mental illness

The inability to cope with life events, which leads to the hypersecretion of corticosteroids, imposes an increased risk for depression, as well as increased abdominal obesity, osteoporosis and cardiovascular problems¹²³. Hypercortisolaemia that is associated

Box 3 | **Stress as a risk factor for depression**

Supporting evidence for the fact that stress might precipitate depression includes the following:

- The hyperdrive of hypothalamic corticotropin-releasing hormone (CRH)/ vasopressin neurons and hypothalamic–pituitary–adrenocortical (HPA) hyper-reactivity that results from chronic stress also occurs in depression.
- Neuroendocrine signs of depression can be discriminated from other stress-induced psychiatric disorders, such as post-traumatic stress disorder (PTSD), which is characterized by CRH/vasopressin hyperdrive and hypocortisolaemia.
- Hypercortisolaemia can disturb anxiety and aggression regulation, and produce cognitive impairment that is associated with a depression-like phenotype.
- Hypercortisolaemia disturbs monoaminergic systems in a manner similar to that observed in depression.
- Hypercortisolaemia causes volume reductions in limbic structures, which are also observed in depression.
- Early-life stress can produce enhanced emotional and neuroendocrine reactivity, which creates a vulnerable phenotype for depression.
- HPA activity is a predictor for the relapse and remission of depressive symptoms.
- Intracerebroventricular CRH induces anxiety and a depression-like phenotype.
- Glucocorticoid receptor (GR) and CRH1 receptor (CRHR1) mutagenesis in mice modulates anxiety, aggression and cognitive performance.
- Antidepressants enhance limbic mineralocorticoid receptor (MR) and GR expression in correspondence with normalization of the HPA axis.
- CRHR1 antagonists ameliorate the signs and symptoms of depression.
- GR antagonists improve psychotic symptoms.
- MR antagonists worsen antidepressant outcome.

This evidence leads to the conclusion that sustained hyperactivity of the HPA axis and MR/GR imbalance precipitated by (early) life stress generate a vulnerable phenotype, which traverses present diagnostic boundaries^{4,9,10}.

with coping problems is primarily related to emotional arousal, psychotic symptoms and cognitive impairment¹²⁴. Hypercortisolaemia that occurs secondarily to pituitary tumours in patients with CUSHING DISEASE or after prolonged glucocorticoid administration is believed to cause similar symptoms. In both depression and Cushing disease, the volume of the hippocampus is reduced¹²⁵, although actual neuronal damage was not detectable in post-mortem brain tissue from individuals with depression¹²⁶.

However, from both the clinical and basic research perspectives, it is important to separate these afflictions, as chronic stress is as different from major depression as it is from Cushing disease. Under conditions of chronic stress, neuropeptides (for example, CRH) trigger corticosteroid secretion. In healthy individuals, neuropeptides coordinate adaptation, but they fail to do so during depression, which precipitates psychopathology. In patients with Cushing disease or those that have undergone corticosteroid therapy, the prime causes are excessive corticosteroid, but not peptide, concentrations, which have effects that range from cognitive impairment to psychosis, although mania and delusions might also occur. Nevertheless, the same endocrine conditions that are elicited by chronic stress and Cushing disease might induce affective disorders in individuals who carry a genetic risk.

CUSHING DISEASE

A hormonal disorder that is caused by prolonged exposure of the body tissues to high levels of cortisol, owing to a tumour in the adrenal or anterior pituitary.

HPA-axis disturbances: risk factors for depression?

Perturbations of the stress system in animals can uncover cognitive and emotional disturbances in predisposed individuals that resemble some of the symptoms that are seen in patients with depression (BOX 3). Further evidence comes from animal models in which components of the HPA axis were modified by mutagenesis. For instance, the *Cre/LoxP* system, under the control of the nestin promoter (*GR^{Nes/Cre}*-knockout mice), induced time-dependent forebrain-specific disrupted expression of GR. These mutants showed some of the neuroendocrine signs of depression, although anxiety and despair were reduced¹²⁷. When *GR*-knockout mice were generated using the α -calcium/calmodulin dependent protein kinase II (α CaMKII) promoter, by deleting the expression of limbic GR (except in the hypothalamic PVN), a robust depression-like phenotype was seen, which was normalized after chronic treatment with the tricyclic antidepressant imipramine¹²⁸. By contrast, forebrain-specific overexpression of *GR* produced a state of emotional lability¹²⁹. Mouse mutants in which the CRH1 receptor (CRHR1) was totally^{130,131} or conditionally¹³² deleted showed a reduction in affective symptoms. These mice, as well as those in which GR function was impaired by *GR*-antisense expression¹³³, implied that components of the HPA axis (such as CRHR1 or MR/GR function) are crucial in the pathogenesis of affective disorders. So, what is the evidence that life events or inadequate HPA function can really precipitate disorders such as depression?

First, there are strong correlative data. Many patients with depression have disturbed HPA-axis regulation. Although hypercortisolaemia often is not obvious from measurements of basal cortisol levels, it is reflected by elevated daily cortisol concentrations in the urine. However, the hallmark is an insufficient suppression of corticotropin and cortisol following a low dose of the synthetic glucocorticoid dexamethasone, and a blunted corticotropin response to CRH. A refined test that combined dexamethasone suppression with CRH stimulation (the dex/CRH test) indicated that CRH and vasopressin both drive HPA activity in patients with depression¹³⁴. This conclusion was indirectly derived from the observation in rats that dexamethasone, when administered at low dosages, acts primarily at the pituitary, and thereby suppresses corticotropin and corticosterone. In the brain, this depletion of endogenous corticosteroid hormone is not compensated by dexamethasone, because at low dosages this drug is a poor penetrator of the blood–brain barrier (BBB)¹³⁵. In support of this mechanism, in animals that are selected for high innate anxiety and excessive hormonal responses to the dex/CRH test, the hypersecretion of corticosterone is normalized by pretreatment with a vasopressin antagonist¹⁰⁴. The elevation of CRH and vasopressin levels is also shown in post-mortem human brains¹³⁶.

Second, longitudinal studies with repeatedly-performed neuroendocrine tests not only showed that patients do not respond well to the treatment if

HPA-axis disturbance persists, but also showed that clinically remitted patients whose HPA disturbance reappears are at high risk of relapse¹³⁷. Apparently, the normalization of HPA disturbances is a prerequisite for successful treatment and persistence, whereas the reappearance of HPA disturbances is prognostically unfavourable. This supports the view that HPA activity is directly involved in the pathogenesis and course of depression. However, it is important to bear in mind that peripheral stress-hormone changes do not necessarily reflect central processes: CRH might be elevated at brain sites that are remote from the hypothalamus, thereby conveying depression or anxiety-like symptoms in the absence of increased plasma cortisol.

Third, in healthy individuals who belong to families with a high genetic load for depression, the combined dex/CRH test showed cortisol responses that were intermediate between those individuals with acute depression and normal controls¹³⁸. This indicates that subtle changes of HPA-axis function are a genetic trait that increases the risk of developing depression or other stress-related diseases later in life. Importantly, this is found in individuals who are not long-term exposed to a clinical setting.

Collectively, these observations support the concept that HPA-axis dysregulation, possibly as a genetic predisposition, is a risk factor for depression. The evidence is reinforced by the finding that antidepressants induce MR and GR to some extent, and possibly also aspects of the BBB (that is, multidrug resistance P glycoprotein)¹³⁹ in parallel with HPA-axis normalization⁹⁸. This raises the question of whether this genetic predisposition is linked to corticosteroid signalling or whether genes that are remote from the axis are involved.

The vulnerable phenotype in humans. On the basis of twin studies, depression has an estimated heritability of 40%¹⁴⁰. As in any complex genetic disease, many different genes seem to be involved, with varying effects on vulnerability. In addition, some individuals who experienced early trauma, such as parental loss, sexual abuse or physical assault in childhood, also present a vulnerable phenotype with an increased risk for neuroendocrine dysregulation later in life^{141,142}. Although genetic factors and early trauma are well-documented antecedents of major depressive episodes that are precipitated by life events or chronic stressors, many people who are exposed to such external influences never develop depression, whereas other patients who have not been exposed to any kind of stressor do.

It is estimated that 10–40% of individuals who have been exposed to extreme trauma, such as the holocaust, combat, rape, abuse or a traffic accident, develop PTSD¹⁴³ and show a large comorbidity with depression. These individuals display elevated CRH levels in their cerebrospinal fluid, but, unlike patients with depression, have lower than normal plasma cortisol concentrations and show higher pituitary sensitivity to the corticotropin-suppressing effects of dexamethasone.

Their cortisol signalling capacity seems to be elevated, so that lower levels of cortisol efficiently suppress HPA function¹¹. This implies that afferent pathways to the core of the HPA axis are exposed to reduced corticosteroid concentrations. Many, but not all¹⁴⁴, psychological and biological data support the hypothesis that “the onset of PTSD is facilitated by a failure to contain the biological stress response at the time of the trauma, resulting in a cascade of alterations that lead to intrusive recollections of the event, avoidance of the reminders of the event and symptoms of hyperarousal”¹¹.

Considerable progress has been made in the characterization of neuroendocrine, emotional and cognitive dysregulations in depression and PTSD, but the pathogenic mechanisms that precipitate these stress-related disorders remain poorly understood. By combining chronic stress models with established risk factors — such as adverse early experience, and genetically selected traits for anxiety and aggression — progress can be made in defining vulnerable phenotypes. This approach is nicely illustrated by a recent pharmacogenetic study, in which patients who carried a specific mutation in the *FKBP5* gene, which encodes a co-chaperone of heat-shock protein 90 (HSP90), responded much faster to antidepressants than a group that did not carry this mutation¹⁴⁵. *FKBP5* contributes to the folding of GR in the cytosol and thereby determines the affinity at which cortisol is bound to its cognate receptor. The genotype that predicted favourable clinical outcome was also associated with lower hormonal response to the dex/CRH test and increased *FKBP5* protein expression. Because *FKBP5* inhibits dephosphorylation, increased expression of this co-chaperone might augment the effect of antidepressants, which act through monoaminergic receptors to activate kinases and, consequently, the phosphorylation of transcription factors¹⁴⁶.

Certain genetic factors might also render individuals resilient to developing affective disorders. This is well illustrated by the polymorphism in the *ER22/23 EK* allele, which is located at the beginning of exon 2 of the *GR* gene. Individuals that carry this polymorphism have a healthier metabolic profile and better cognitive function than the general population¹⁴⁷. The polymorphism is also associated with a more favourable treatment outcome in individuals with depression (E. F. van Rossum, personal communication). By contrast, individuals with other functional polymorphisms in the *GR* gene have more body fat, less lean mass, hypersensitive insulin secretion and increased cholesterol levels^{147,148}. The latter group displayed an enhanced corticotropin and cortisol response to a psychosocial stressor compared with controls, which indicates a role of minor genetic variations in the *GR* gene on HPA regulation and related features¹⁴⁹.

At present, the evidence indicates that the nature and timing of the stressor, in combination with genetic risk factors, determine the neuroendocrine and psychopathological features that ensue. An individual who carries a genetic risk for developing a stress-related disease is more likely to develop a

clinical condition in response to threatening events. A notable example is the functional polymorphism in the promoter region of a key gene, the 5-HT transporter. Epidemiological studies showed that a traumatic event was less likely to precipitate depression in individuals who carried one or two copies of the short version of the 5-HT transporter than in individuals with the longer version¹⁵⁰. So far, this is the best-documented example of a functional polymorphism in affective disorders.

Therapeutic perspectives. As overexposure of brain tissue to stress hormones has an important role in the development and course of depression, this knowledge might be used for new treatment strategies. This approach was adopted recently in a genetic strategy to attenuate neuronal damage that resulted from excess GR activation in a rat model¹⁵¹. Positive results were obtained with the overexpression of a competing inactive GR variant or a corticosterone-degrading enzyme (11 β -hydroxysteroid dehydrogenase)¹⁵². However, the most effective approach was the delivery of a chimeric receptor that combined the ligand-binding domain of the GR with the DNA-binding domain of the oestrogen receptor, thereby converting the glucocorticoid signal into a genetic oestrogen effect. The expression of the chimeric receptor achieved a reduction in hippocampal lesion size of 63% and rendered excess glucocorticoids protective rather than destructive¹⁵¹.

In the psychiatric realm, diminishing GR- or CRH-mediated actions in depressed patients also had beneficial effects^{153,154}. Preliminary evidence indicates that psychotic symptoms are ameliorated by GR antagonists in psychotic depression, which is a subtype that is characterized by high cortisol levels^{155,156}. Symptoms of steroid psychosis in patients with Cushing disease also respond favourably to GR antagonists¹⁵⁷. In animal studies, chronic GR-antagonist treatment improved cognitive performance¹⁵⁸, enhanced HPA reactivity and led to increased hippocampal MR expression¹⁵⁹. The clinical relevance of MR function during depression was further emphasized in a study in which spironolactone, which is an MR antagonist, worsened the clinical outcome when administered in conjunction with antidepressant treatment¹⁶⁰. Finally, based on the rationale that endogenous cortisol provides an inadequate signal to contain the stress reactions of PTSD patients, pilot studies showed that cortisol administration ameliorated PTSD symptoms^{161,162}. These findings support the

idea that in humans, as in animal models, reinstating appropriate HPA signalling seems to be a promising treatment approach.

Concluding statements

Corticosteroid hormones are important mediators of the response to stress, which is shaped by both genetic endowment and external (early life) factors. The actions of these steroids are enormously diverse, and are mediated by a binary receptor system that, among others, involves MRs and GRs. The two receptor types mediate a finely balanced mechanism that governs the often opposing molecular and cellular changes. Their proper function determines the capacity of an organism to contain the initial stress reactions in the acute phase and the binary system is also crucial in the management of the late recovery phase. In this review, emphasis has been put on the afferent input from limbic networks that conveys purely psychological stress reactions to the HPA axis. It is in this interplay of limbic inputs from the hippocampus, pre-frontal cortex and amygdala with the HPA-axis activity that a vulnerable phenotype for mental illness might evolve.

Stress-related disorders, such as depression and PTSD, are complex and multifactorial: they cannot be attributed to mutations in a single gene or to a single external event, but, rather, result from the concerted actions of many subtle genetic polymorphisms and external events, the effects of which might accumulate over time. Once traumatic life events, in combination with genetic disposition, have engrained long-lasting changes in MR and GR signalling, a vulnerable phenotype emerges. The vulnerability of an individual is defined at three different levels: the traditional clinical phenotype (emotional reactivity and personality); the functional phenotype (neuroendocrine reactivity to stimuli); and the genotype (for example, polymorphisms in genes that are involved in HPA signalling or monoaminergic and peptidergic neurotransmission).

An integrated approach that analyses patients at all three levels leaves room for optimism that not only an understanding of the causation of stress-related diseases, but also new targets for treatment will become available. Importantly, such an approach will provide opportunities for disease prevention, which could make individuals with increased vulnerability more resilient to the adversities and stressors of life.

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Competing interests statement

The authors declare **competing financial interests**: see Web version for details.

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