The cortisol switch between vulnerability and resilience

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EXPERT REVIEW

The cortisol switch between vulnerability and resilience

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In concert with neuropeptides and transmitters, the end products of the hypothalamus-pituitary-adrenal (HPA) axis, the glucocorticoid hormones cortisol and corticosterone (CORT), promote resilience: i.e., the ability to cope with threats, adversity, and trauma. To exert this protective action, CORT activates mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) that operate in a complementary manner -as an on/off switch- to coordinate circadian events, stress-coping, and adaptation. The evolutionary older limbic MR facilitates contextual memory retrieval and supports an on-switch in the selection of stress-coping styles at a low cost. The rise in circulating CORT concentration after stress subsequently activates a GR-mediated off-switch underlying recovery of homeostasis by providing the energy for restraining the primary stress reactions and promoting cognitive control over emotional reactivity. GR activation facilitates contextual memory storage of the experience to enable future stress-coping. Such complementary MR-GR-mediated actions involve rapid non-genomic and slower gene-mediated mechanisms; they are time-dependent, conditional, and sexually dimorphic, and depend on genetic background and prior experience. If coping fails, GR activation impairs cognitive control and promotes emotional arousal which eventually may compromise resilience. Such breakdown of resilience involves a transition to a chronic stress construct, where information processing is crashed; it leads to an imbalanced MR-GR switch and hence increased vulnerability. Novel MR-GR modulators are becoming available that may reset a dysregulated stress response system to reinstate the cognitive flexibility required for resilience.

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Treatment of stress-related disease should not be particularly causal or symptomatic, but a treatment based upon the imitation and perfection of Nature's autopharmacology (Hans Selye).

INTRODUCTION

In their book 'Endocrine Psychiatry: the riddle of melancholia', Edwin Shorter and Max Fink recall the rise and fall of the dexamethasone suppression test (DexST) for assessment of major depressive disorder (MDD), and implicitly the discipline of Endocrine Psychiatry [1]. The DexST exploits resistance to corticosterone and cortisol (rodents only corticosterone, collectively called CORT) feedback in the hypothalamus-pituitary-adrenal (HPA) axis which is a characteristic symptom for some but not all individuals suffering from MDD [2]. The test gained further precision to predict remission and relapse if escape of ACTH and CORT release from Dex suppression was amplified by a CRH challenge [3]. While the Dex-CRH test became a powerful research tool (Box 1), the DexST did not become a routine test: too expensive, laborious, and a poorly understood connection to the widely divergent depression symptomatology. However, as was stated (John Greden, page 98) [1]. "*Our country -(i.e. the USA)- got a bit too occupied that the DexST is a lab test. In actuality ….. it rather is a reflection of what's going on in the brain*".

Despite this equivocal start of the DexST in the clinic, the presumed link between stress hormones and psychiatric symptoms has never left the scene. Meanwhile, research on stress-adaptation per se moved on [4]. CORT, initially, was thought to mediate the effects of stress, simply because hormone levels increase after exposure to a stressor [5]. Then, it was noted that CORT rather *protects* against damage caused by an overshoot of the primary stress (defense) reactions themselves [6]. Circulating CORT rises in concentration within minutes and dampens the impact of its initial trigger –e.g. CORT suppresses the pro-inflammatory reaction to tissue damage, immune reaction to infection, and psychological reaction to threat–, in a mechanism that is fundamental for the adaptive process or allostasis [4]. But, as will be pointed out in our contribution, this dampening protective effect of CORT against the primary stress reaction (the *'off* switch') is only half the story. CORT also participates in the '*on* switch' of the stress reaction.

In a recent Molecular Psychiatry expert review on stress-related disease, Agorastos and Chrousos focused on CORT [7]. The authors not only extended the stress and allostasis vocabulary with cacostasis, eustasis and hyperstasis concepts. They also convincingly argued that the vulnerable 'stressed out' state characterized by high CRH and potentiated by vasopressin release from the hypothalamic paraventricular nucleus (PVN) may precipitate a

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*hyper*cortisolemic '*acute stress syndrome*' as observed in MDD and generalized anxiety disorders. In a hypothetical model, this state of *excess* cortisol is thought to shift over time in some individuals to a *hypo*cortisolemia-linked '*acute sickness syndrome*' due to presumed (adrenal) exhaustion. Hypocortisolemic pathologies are e.g. post-traumatic stress syndrome (PTSD), atypical depression, fibromyalgia, and chronic fatigue syndrome. The glucocorticoid receptor (GR), encoded by the NR3C1 gene, was highlighted as a potential mediator of this hypothetical pathogenic switch [8]. The simple concept of escape from dexamethasone suppression in a DexST would fall short when facing this more complex spectrum of CORT-related psychopathology.

Here we take the theory of Agorastos and Chrousos one step further and will not only focus on the hormone CORT acting via GR but rather approach the role of CORT in stress and psychiatry from the perspective of its actions via two receptor types: GR and the mineralocorticoid receptor (MR). Of note, the action of CORT as the end product of the HPA axis, occurs in concert with numerous stress-related signaling systems, driven by CRH/vasopressin and pro-opiomelanocortin (POMC) and in interaction with neurotransmitters, neuropeptides, growth factors/cytokines and other hormones [9–11]. Actions by CORT are pleiotropic and sexually dimorphic but can gain specificity by the context in which they occur.

We will argue that CORT controls coping with and adaptation to change (allostasis) by a receptor-mediated *on*- and *off* switch, that -at the level of the organism as a whole- needs to be in balance for providing the energy in maintaining homeostasis and health. Accordingly, this action of CORT in coordinating, integrating, and controlling defense reactions and adaptation to stress is crucial to provide the energy for resilience, i.e. the ability to cope and adapt in the face of threats, adversity, and trauma [12]. Our contribution is a tribute to Bruce McEwen, who discovered CORT receptors in the hippocampus [13].

Box 1. Dexamethasone

The brain Dex story evolved when ERdK tried in early 1969 to reproduce the retention of ^{3}H-corticosterone by hippocampal nuclear receptors with the much more potent synthetic glucocorticoid. However, no success, neither in The Netherlands as a Ph.D. student nor as a post-doc in Bruce McEwen's laboratory [233]. Rather, Dex was retained in pituitary corticotrophs. That Dex targets the anterior pituitary rather than the brain is fundamental for understanding the potent suppressive action on stress-induced pituitary ACTH release underlying the DexST and Dex-CRH test. The latter test has been leading in the exploration of the basic mechanism underlying the pathogenesis of PTSD and depression, and the action of antidepressants [234–236].

Dex, prednisone, and even to some extent cortisol, but not corticosterone, are substrates for P-glycoprotein and are exported from the brain [237] (Fig. 1). Pharmacotherapy with Dex and synthetic analogs is symptomatic, but its success is limited by side effects. For instance, if used as an immunosuppressive agent, this also suppresses the HPA axis, resulting in adrenal atrophy and a myriad of serious physical and psychological side effects [238]. The brain is poorly penetrated by these synthetic analogs however and, worse, causes depletion of endogenous CORT, which impairs MR functioning [217]. In humans, Dex may cause slow-wave sleep disturbance, euphoria as well as dysphoria; clinically, 30% of the children receiving Dex developed sleep deficits and aberrant neuropsychological symptoms. These adverse effects of Dex can be attenuated by restoring MR-GR balance [40, 217].

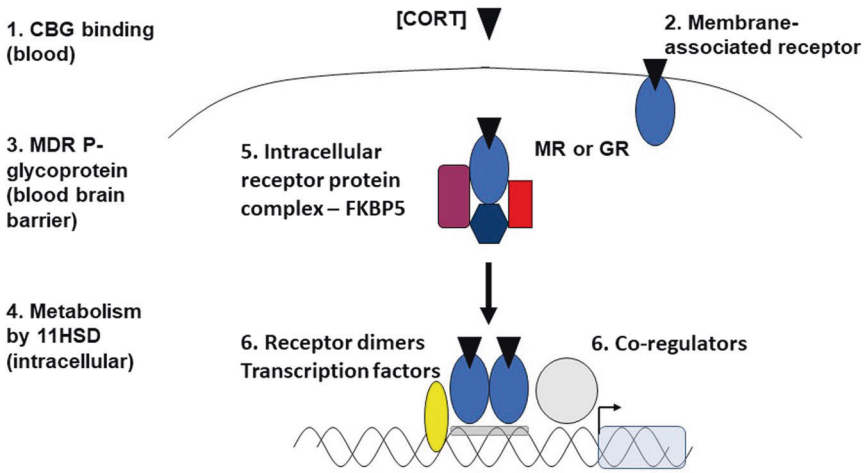

Fig. 1 CORT action. 1. CORT circulates bound to corticosteroid-binding-globulin (CBG). 2. CORT exerts rapid non-genomic actions via putative membrane-associated receptors: MR activation stimulates the presynaptic release of glutamate and excitatory transmission and GR activation stimulates the postsynaptic release of endocannabinoids that exert transsynaptic inhibitory control over excitatory or inhibitory transmission [224]. 3. Access to the brain of 17-OH molecules, cortisol, and synthetic steroids such as Dex, but not corticosterone, is hampered by ABCB1 or MDR-1 (multiple drug resistance p-glycoprotein 1) in the human blood-brain barrier. In contrast, the human ABCC1 or MRP-1 (multidrug resistance-associated protein 1) exports corticosterone (lacking 17-OH) rather than cortisol from adipose tissue, skeletal muscle, and the pituitary. In rodents two Abcb1 isoforms – Abcb1a and Abcb1b- exist, the former being the one abundantly expressed in the blood-brain barrier [225, 226]. 4. The other gatekeeper is the intracellular oxidoreductase 11β-hydroxy steroid dehydrogenase (11-HSD) that determines MR's physiological function. In polarized epithelial cells, such as in the kidney and colon, 11-HSD type 2 is expressed [17]. This is an oxidase that degrades CORT, thus making these cells aldosterone-specific. 11-HSD-2 and thus Aldo-MR is highly expressed in specialized neurons in the brain stem N. tractus solitarius (NTS) which enables Aldo to regulate salt appetite and associated functions of motivation, reward/disgust, but also higher functions in emotional arousal and cognitive functions, such as e.g. spatial learning. Aldo-MR also seems to occur in circumventricular organs and vascular endothelial cells [227]. Patients suffering from Conn's syndrome and hyper-aldosteronism show depression and anxiety disorders, a condition that can be mimicked in animal models [228, 229]. In most of the brain, heart, and adipose tissue, 11-HSD-1 regenerates CORT. This local regeneration plus the much higher circulating CORT concentration renders in the brain a 100–1000 fold excess over aldosterone. Accordingly, these are the CORT-MR where CORT rather than aldosterone is the principal ligand [17]. 5. MR and GR are part of multimeric proteins from which the receptors are released upon CORT binding for nuclear translocation and regulation of gene transcription. FKBP5 is one such chaperone [94]. 6. Interaction with transcription factors and coregulators occurs at the DNA/chromatin level and determines the nature of the CORT signal binding to (glucocorticoid response element) GRE; the composition of the TF and coregulator cocktails depends on context, i.e. other signaling pathways stimulated by e.g. transmitters, neuropeptide, growth factors, and cytokines. MR and GR may form homo- or heterodimers, at least depending on the CORT concentration [197, 230]. Nuclear acceptor sites may show a larger capacity for MR- and GR than predicted by the limited binding capacity of the receptor proteins [196].

A ONE HORMONE DUAL RECEPTOR CONCEPT

CORT's fundamental role in stress-coping and adaptation has its roots in Selye's pendulum hypothesis, which states that "*an absolute or relative excess or deficiency of mineralocorticoids vs glucocorticoids could set disease susceptibility at different levels* [5]. This hypothesis was based on the animals' exposure to a pharmacological concentration of the weak mineralocorticoid deoxycorticosterone that acts pro-inflammatory, provided the animals were also offered a high NaCl solution for drinking as a conditioning factor. In such a pro-inflammatory context, high concentrations of CORT subsequently exerted anti-inflammatory actions.

To understand this, it is important to know that CORT not only activates GR but also its phylogenetic predecessor, the MR, encoded by the NR3C2 gene [14] which was cloned by Ron Evans et al. [15]. MR is promiscuous and binds with high affinity, besides CORT, the mineralocorticoids aldosterone, deoxycorticosterone as well as progesterone [16]. The binding specificity of MR for aldosterone is determined by the oxidoreductase 11β-hydroxy steroid dehydrogenase type 2 (11-HSD-2; Fig. 1) [17, 18].

The most fundamental aspect of MR-GR cooperativity is the difference in affinity to the prevalent agonist CORT. GR affinity to CORT is rather low; accordingly, GR becomes only largely occupied during the circadian peak and after stress. Conversely, MR has a very high affinity for CORT, so that it is already substantially occupied at rest [19]; incidentally, this MR is the (Dex-unresponsive) receptor discovered in 1968 by Bruce McEwen [13]. MR and GR specificity is also determined by e.g. transcription factors (for example NeuroD) [20] and coregulators [21].

Upon binding of CORT, MR and GR translocate to the nucleus where they act as transcriptional regulators. These gene-mediated actions by CORT take at least 30 min to develop and may last for days or even a life-time in the case of developmental programming [22]. In addition, lower-affinity MR and GR -of which the exact mechanism so far remains somewhat elusive- mediate rapid (minutes) non-genomic CORT actions [23–26]. MR is highly expressed particularly in some limbic regions, notably the hippocampus and septum, as opposed to the more ubiquitously high expression of GR. However, most brain cells contain low and detectable MR [27].

Thus, while Selye's pendulum hypothesis was based on adrenally-secreted mineralocorticoid and glucocorticoid hormones, CORT by itself can fulfill this dual role in the brain, by activating MR and GR. Accordingly, this has led to the hypothesis that "*upon an imbalance of MR- and GR-mediated actions, the initiation and/or management of the stress response becomes compromised. At a certain threshold, this may lead to a condition of neuroendocrine dysregulation and impaired behavioral adaptation, which potentially can aggravate stress-related deterioration and promote vulnerability*" [28]. See also [29–31]. This hypothesis refers to the limbic-associated cognitive, emotional, and neuroendocrine processes where both receptors are abundantly expressed.

ROLE OF TWO RECEPTORS IN CIRCADIAN VARIATION

CORT levels peak around the start of the active period when the hormone acts in a pro-active manner to prepare for the upcoming day. At that time GR and MR are both occupied. CORT level is low around sleep onset and at nadir predominantly MR is activated [32]. Central MR blockade increases both circadian CORT trough and peak levels; GR blockade increases the circadian peak levels only and thus the amplitude in circadian variations [33–35]. Accordingly, MR rather than GR activation is important for the *tone or setpoint* of the basal CORT rhythm [36].

The circadian rhythm overarches ultradian CORT pulses every 1–2 h [32]. The affinity of CORT to MR is high enough to maintain its nuclear localization over the subsequent pulses. However, CORT dissociates from GR between the pulses and activates gene transcription every hour. This hourly gene pulsing is a prerequisite for the maintenance of tissue responsivity to CORT [37, 38]. Ultradian pulses are also necessary to allow synaptic plasticity -important for memory formation- to take place when the organism enters its active phase [39].

In humans, Born and colleagues demonstrated complementary MR- and GR-mediated actions on memory processes during the night. At the circadian trough, during slow-wave sleep, predominant MR occupancy was found to promote the reactivation of hippocampal memories. Additional GR activation impairs this process [40, 41]. Interestingly, during day-time CORT exerts the opposite effect on mnemonic processes: predominant MR occupancy facilitates memory retrieval, while GR promotes memory consolidation (see next section). CORT actions, therefore, seem to depend on the *brain state*; during rest, when predominantly MR is activated, CORT promotes the recapitulation of events from the past [42], while active states are characterized by MR-dependent retrieval and GR-dependent consolidation of new information. Related to the former, Liston et al. [43] showed in rodents that low levels of CORT during the inactive period, through MR-dependent pruning of older cortical spines, optimize more recent GR-mediated learning and memorizing of a motor task.

The circadian variation in circulating CORT level also correlates with the detection and perception of sensory signals, including sound, smell, and taste [44]. With low CORT levels during sleep-onset, the ability to detect a sound is increased at the expense of the interpretation of its meaning. Rising CORT concentrations activating GR during the active period improve the perception-discrimination-ability, i.e. the ability to interpret accurately the meaning of sensory signals [45]. An impaired perception of sound, taste, and smell is well-known for adrenally-deficient Addison patients. This decrease in perception-discrimination-ability occurs although patients can detect sensory stimuli much better than adrenally-intact individuals. Detection and perception thresholds are restored with CORT or prednisone substitution, but not with mineralocorticoids, suggesting GR dependency [44].

The circadian variation in the detection and perception of sensory stimuli has obvious consequences for the processing of acute stressors. Thus, at rest, the lower detection threshold will more readily alert for acute danger. In contrast, during the active period, the improved perception imposed by GR activation will assist in the prediction of potential acute stressors.

ROLE OF TWO RECEPTORS IN ACUTE STRESS

In discussing the effects of acute stress via two receptors, we focus particularly on regions like the hippocampus where both MR and GR are abundantly expressed [19]. The dual expression pattern (mostly in limbic regions) implies that MR, alone or at higher CORT concentration in interaction with colocalized GR, is implicated particularly in contextual aspects of coping with a social, emotional, and cognitive challenge. It is important to realize, though, that the individual's overall response to stress is a composite of the response of all brain circuits (and coordinated actions of all organs), some of which will be particularly affected through GR and others through both MR and GR, or even MR alone.

MR: memory and coping style

Acute stressors trigger an immediate alarm reaction and activate the CRH-PVN neurons engaged in the organization of the rapid sympathetic/behavioral fight-flight-fright response and slower HPA-axis activation (Fig. 2**)** [46]. MR blockade attenuates the stress-induced sympathetic and blood pressure response, attention, and vigilance, but enhances the CORT response [33, 34, 47, 48]. Thus, systemic, intracerebroventricular (icv), or intrahippocampal MR antagonist treatment increases basal activity

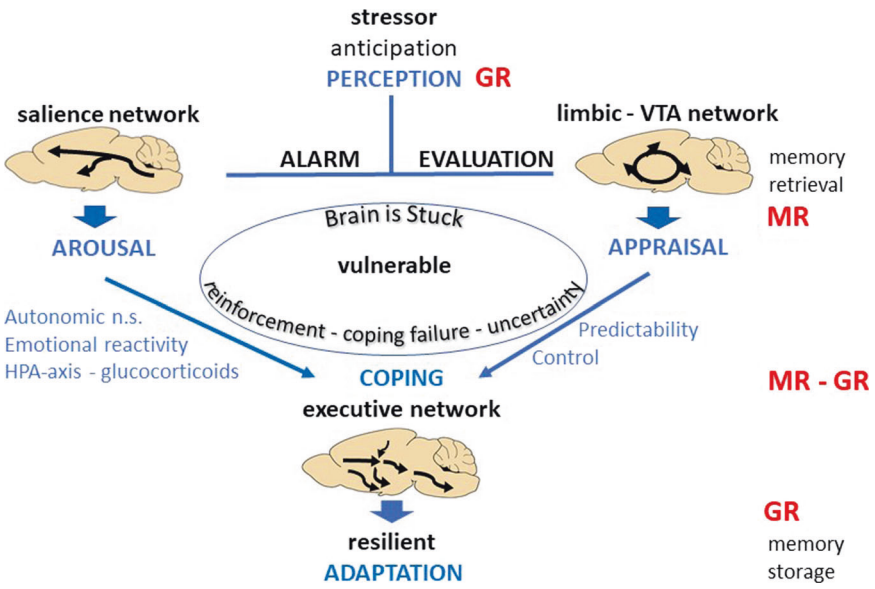

Fig. 2 Stress: from perception to adaptation. CORT modulates the processing of information from perception to coping and adaptation in a complementary manner via MR and GR. Perception depends on GR activation during the circadian cycle. MR-mediated action in the brainfacilitates memory retrieval, risk assessment, and response selection, and participates in the selection of coping styles to save energy. Subsequent CORT activation of GR promotes contextualization in support of memory consolidation. CORT allocates energy resources to circuits in need during stress coping and adaptation and promotes energy storage at rest. The actions exerted by CORT on information processing are conditional and time-dependent, and therefore should be considered in the context of CRH/vasopressin-driven HPA-axis, sympathetic and behavioral reactivity in concert with multiple dedicated signaling cascades. Vulnerability vs resilience depends on coping and adaptation in which the balance of MR- and GR-mediated actions is thought relevant. If coping fails 'the brain may get stuck' as a sign of a 'chronic stress construct', a condition characterized by habitual behavior, rumination, or compulsivity [22, 102, 202, 211]. The salience, appraisal, and executive networks (see sagittal sections) are being unraveled and stress-induced plasticity is documented [83, 119, 127]. During chronic stress conditions, top-down control of mPFC and hippocampal circuits over the emotional brain diminishes because of neuronal atrophy [109]. Cartoon generated after discussion with Pieter Smelik and Bruce McEwen.

and the *peak* of stress-induced HPA-axis activation, probably through diminishing the inhibitory tone of neural input to the PVN. After stress, GR-mediated feedback controls the *duration* of the HPA-axis response.

Pharmacological and genetic studies have demonstrated that hippocampal MR blockade causes an anxiolytic, anti-aggressive phenotype [49–52]. This response likely is in part under the control of the hippocampal CA2 neuronal network (Box 2) [53]. Paradoxically, overexpression of MR in the amygdala was also found to be anxiolytic [54–56]. Nevertheless, this makes sense considering that the hippocampus exerts a suppressive influence on the HPA axis, while the amygdala stimulates the axis. Similar features of MR are evident from genetically selected animal lines, e.g. wild house mice selected for their short attack latency (SAL), as compared to long attack latency (LAL), and Roman high and low avoiders [57, 58]. These studies showed that high hippocampal MR expression relates to a rigid internally organized *pro-active* coping style characterized by a low CORT and high sympathetic fight response in case of social conflict as opposed to the low MR-linked *reactive (flexible)* phenotype. The latter phenotype is better equipped -thus more resilient- than its dominant congener in coping with stressors in a novel environment.

MR blockade impairs spatial and contextual *memory retrieval* in the Morris water maze and fear-conditioning paradigms [59, 60]; the reverse is observed with the genetic enhancement of hippocampal MR function [55]. These studies show that MR promotes rigid perseveration of learned behavior. To better understand MR's role in cognitive functioning and behavior an animal model was generated with MR forebrain overexpression (MRhi) and simultaneous GR underexpression (GRlo) [61]. Two lessons were learned. Firstly, MRhi mice show the highest suppression of stress-induced HPA-axis activity, especially when combined with GRlo. Secondly, the MRhi/GRlo mutants displayed enhanced perseveration of learned behavior in searching an escape route in a water maze and a fear-motivated passive avoidance paradigm. Collectively this demonstrates that the MR-GR balance is important for cognitive flexibility.

That MR activation affects search *strategy*, was demonstrated in the 'circular hole board'. In this test, the animals can select either a costly *spatial (cognitive)* strategy to collect a reward or a simple energy-conserving *stimulus-response (habitual)* routine. While most male rats normally use a spatial strategy, part of them switched to habitual behavior when exposed to a mild stressor or CORT injection. The stress-induced switch depends on MR because it could be blocked with an MR antagonist [62, 63].

An MR-dependent shift from a cognitive to a habitual coping style was also demonstrated by Lars Schwabe et al. in humans [64, 65]. Moreover, individuals carrying a gain-of-function genetic MR variant generally prefer the habitual stimulus-response pattern linked to dorsal striatal connectivity rather than the spatial-oriented hippocampal function [66], as was observed with fMRI and EEG. This MR gene variant is based on 2 single-nucleotide-polymorphisms (SNP) in the promoter region, 2G/C (rs2070952) and I180V (rs5522), that were examined in a haplotype approach. The MR gain-of-function variant (haplotype 2, frequency 41%) was found to be associated with better stress handling and rapid HPA-axis peak activation [67]. Higher dispositional optimism, less rumination, and reduced thoughts of hopelessness were found in female haplotype 2 carriers [68]. They also appeared protected against negative mood effects of variations in sex steroids during the reproductive cycle and oral contraceptive use [69]. Interestingly, a sex-dependent role of early life adversity in vulnerability to depression was also established for carriers of these MR gene variants [70, 71].

Box 2. MR: New attention for an old receptor

Four key observations in recent years further highlight the importance of MR.

Firstly, McCann et al. [53] discovered that MR is a 'terminal selector' transcription factor in determining the molecular and functional phenotype of hippocampal CA2 pyramidal neurons. MR deletion - in the embryonic MR ^{NesCre} whole brain mutant, the postnatal MR^{Am2Cre} variant or following acute viral MR knockdown in the hippocampus, hampered the functioning of the CA2 neurons, and thus the whole hippocampal tri-synaptic circuit, as is apparent from a deficit in contextual learning, object and social recognition and discrimination [183, 197]. These hippocampal cells express also oxytocin- and V1B receptors, which have a certified function in these aspects of social behavior.

Secondly, Mifsud et al. reported, using genome-wide ChIP-seq and Ribo-Zero RNA-seq, that MR affects the expression of more than 50 ciliary genes [196]. The ciliary gene control appeared to be critical for the differentiation of human fetal neural progenitor cells (hfNPCs) in dentate gyrus neurons. Dentate gyrus apoptosis and reduced neurogenesis, earlier observed after ADX also occurred after MR forebrain deletion and were rescued by MR activation. While MR is required for neurogenesis, GR affects the proliferation and migration (positioning) of the newborn cells [239].

Thirdly, Hartman et al. [195] discovered that MR activation in mouse hippocampus downregulates GR activity via induction of FK506-binding protein 51 (FKBP5), a receptor co-chaperone. FKBP5 not only responds to MR activation but also during stress as part of a GR ultrashort feedback loop induced by the rising CORT levels. That MR regulates FKBP5 expression is important since MR can thus tune GR functioning. Overexpression of FKBP5 in CRH neurons produces CORT resistance, causing disinhibited HPA-axis activity; conversely, enhanced feedback suppression occurs when FKBP5 is deleted [240]. Accordingly, FKBP5 (epi)genetic variation is associated with the outcome of the Dex/CRH test and, potentially, MDD risk [93], a finding that is fundamental for the FKBP5 model in understanding how Gene X Environment interaction contributes to the etiology of psychiatric disorders [94].

Finally, MR not only affects the stress response via transcription but also non-genomically. Both in the hippocampus and basolateral amygdala, MR quickly increases spontaneous glutamatergic transmission [24, 81]. The MR-dependent activation may contribute to memory encoding effects through MR, especially of emotionally salient information [241, 242].

These novel findings demonstrate that CORT action via MR is a determinant of the hippocampal phenotype, modulates neurogenesis, and tunes GR activity via FKBP5. Moreover, MR-induced excitability is suppressed by GR activation in the hippocampus, but enhanced in the amygdala, which is at the root of the appraisal process underlying the switch in coping strategy during stress.

Box 3. CORT metaplasticity

During acute stress, neurons are exposed to multiple waves of stress hormones, starting with monoamines and peptides and slightly later CORT. Elevated levels of these stress mediators normalize over 1-2 h. Under some circumstances, the same cells might be hit again by stress hormones, e.g. in case of a renewed stressor. Several studies over the past decade have shown that particularly amygdala cells (more so than e.g. hippocampal cells) respond differently to a successive rise in CORT level, a phenomenon dubbed 'metaplasticity' [81]. For instance, amygdala cells show a rapid MR-mediated sustained increase in spontaneous glutamatergic transmission when exposed to the first pulse of (100 nM) CORT. A similar pulse 1 h later causes a rapid *decrease* in spontaneous glutamate transmission, now through GR. Such decreased glutamatergic transmission in the amygdala was also observed in mice that were stressed before CORT administration in vitro.

While our review describes many cellular and behavioral effects after a single acute stressor, it is good to keep in mind that different effects might emerge under circumstances where stressful events come in clusters. Metaplasticity may even be relevant for single, acute stressors since it was also demonstrated in vitro during a succession of β-adrenoceptor activation by isoproterenol and CORT administration, as happens during stress [242]. Finally, the phenomenon of metaplasticity is relevant for the peak of the circadian rhythm when CORT is released in hourly (ultradian) pulses [243]. It was shown that pulses of increasing or decreasing amplitude have a strong influence on the interpulse excitability of amygdala cells. This in turn may partly explain why the effectiveness of fear conditioning differs during the various phases of the circadian rhythm.

Conversely, the rs5522 SNP, located in exon 2 of the MR gene, was found to be associated with depressive symptoms, heightened threat-associated amygdala reactivity, and deficits in stress-induced reward learning [72]. These associations together with the reduced MR gene expression in the post-mortem brain of depressive patients [73, 74], highlight MR as a key receptor in resilience [75, 76].

GR: memory consolidation and adaptation

In rodents, spatial memory consolidation, measured 24 h after learning, is impaired in adrenalectomized (ADX) animals and restored after CORT replacement. The contextual memory deficit after ADX is caused by a dysfunctional GR since it is also observed after post-learning administration of the GR-antagonist mifepristone (100 ng icv) as well as in mutant mice lacking GR-DNA binding [59, 77, 78]. Also in fear-motivated behavior, GR activation promotes contextual memory consolidation but this requires additional norepinephrine (NE) stimulation in the amygdala [79]. This synergism of NE-cAMP and GR activation seems to proceed via a rapid non-genomic endocannabinoid mechanism that disinhibits GABAergic control in the amygdala [80] and is further enhanced by MR-GR-mediated metaplasticity (Box 3) [81]. Animals without adrenal medulla have impaired fear memory consolidation unless exogenous NE is administered.

The fear-motivated behaviors are usually based on an electric shock triggering a *reactive* stress response (similar to e.g. a cold or painful physical stressor), that can directly activate the PVN-CRH neurons via various ascending brain stem pathways [82, 83]. In higher brain regions, cells and networks activated by the psychological aspects of such a footshock experience were recently revealed in 4D [84]. One of the networks overlaps with the network of sparsely distributed stress-induced c-fos positive neurons earlier described by Hans Reul's group, after exposure of rats to the forced swim test (FST). This CORT-GR activated c-fos pattern in the hippocampus dentate gyrus, part of an engram, was found indispensable for memory storage of passive coping behavior; engram refers to a sparse set of interconnected neurons, sometimes distributed over several brain regions, that is linked to a specific and lasting memory. Administration of a methyl-donor impaired GR-dependent memory performance and attenuated c-fos expression in the memory engram while hampering the ERK1/2–MSK1–Elk-1 signaling pathway suggesting the involvement of an epigenetic mechanism [85, 86].

A similar c-fos positive hippocampal memory engram was found in a fear condition paradigm [87]. CORT administration further increased the engram marker in parallel with cue rather than context-dependent memory function suggesting fear generalization. Following the attenuation of engram excitability by chemogenetics, contextual memory performance was reinstated. The study is in line with previous observations on the role of excess CORT-GR activation in fear generalization involving tPA (tissue plasminogen activator), which blocks the hippocampal BDNF-Erk1 cascade [88]. Fear generalization is considered a model for PTSD.

Genetic deletion of GR from the male rat forebrain except for PVN and central amygdala produced a phenotype characterized by increased anxiety-like behavior and passive coping. Circadian peak and stress-induced CORT levels were increased, which coincided with the escape from Dex suppression and increased PVN-vasopressin release. Collectively, this phenotype suggests a rat model displaying vulnerability to stress [89]. Deletion of GR from the central amygdala revealed deficits in cue and context-dependent fear conditioning that could be ameliorated with CRH [90]. GR deletion from PVN neurons enhanced stress-induced HPA-axis activity [91]. HPA-axis hyperactivity, reduced anxiety, and fear-motivated behavior was displayed by male mice if GR was deleted in glutamatergic excitatory neurons, but not in GABAergic inhibitory neurons. The mutants showed reduced electrophysiological responses in the basolateral amygdala (BLA). Subsequent viral knockdown of GR showed that fear expression is affected [92]. These animal studies suggest an important role of GR-expressing forebrain excitatory neurons in the pathology of anxiety disorders.

Regarding genetic variation in the GR gene, the BclI (rs4142347) and ER22/23EK SNPs are associated with vulnerability to MDD, the latter also with GR resistance and clinical response to antidepressant treatment. BclI and N363S (rs6195) gene variants associated

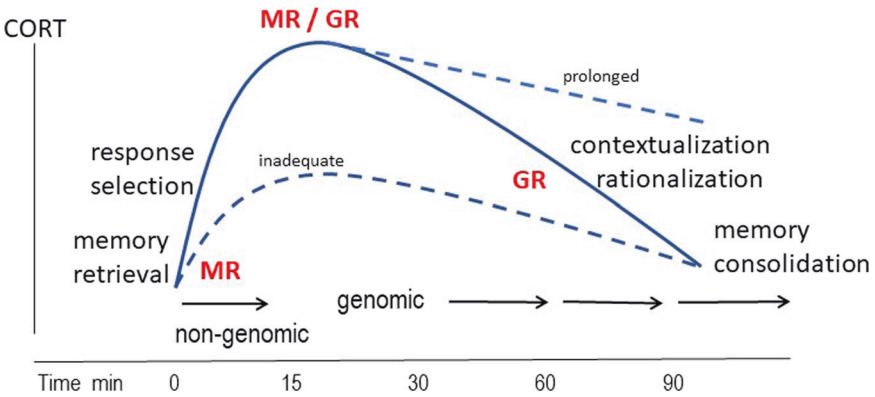

Fig. 3 CORT and the stress response. "Stress is a composite, multidimensional construct, in which three components interact: (i) the input when the stressor is perceived and appraised as a threat to homeostasis, (ii) the processing of stressful information, and (iii) the output or stress response. The three components interact via complex self-regulating feedforward and feedback loops to restore homeostasis through behavioral and physiological adaptations" [149]. Depicted is a typical stress response where memory retrieval and response selection (coping) are facilitated by MR activation, while subsequently with higher CORT concentrations additional GR-mediated action promotes contextualization, memory consolidation, and recovery (adaptation). Broken lines indicate variation in either MR-dependent peak and/or GR-dependent duration of CORT secretion. It is important to realize that CORT measurement at a one-time point in blood plasma or saliva, is not informative because of the rapid variation in CORT levels by accidental stressors and ultradian changes. Rather, patterns need to be measured in blood and saliva, such as the stress-induced CORT (and ACTH) response, e.g. the Trier Social Stress Test [231]. The area under the curve (AUC) CORT level is increased during MDD and decreased during PTSD, and there are sex differences [106, 194]. CORT tissue concentrations can be measured with microdialysis [32]. At a longer time scale, one can measure e.g. cumulative secretion of CORT and its metabolites in 24 h urine and hair [232].

Box 4. Chronic stress models

Chronic stress models in rodents are based on the idea that the rat suffers from daily inescapable and uncontrollable and unpredictable conditions. These conditions may be evoked even by a single prolonged stress procedure [244]. Related to that is the learned helplessness model: lack of control causes mPFC activation of the dorsal raphe 5HT system, which activates the vlPAG involved in passive coping. There seems no CORT involved in this rapid switch, and animals in the learned helplessness model have to learn to gain back control [132].

The various chronic stress paradigms vary in context [245]. Chronic (daily) restraint stress (CRS) is based on subjecting the animals daily to the same procedure to which the animal adapts or habituates. This is less so in the chronic mild, unpredictable stress (CMS) paradigm, which is based on the assumption that a random presentation of the stressors makes the procedure unpredictable, although at the end of the day the animals are rescued by the experimenter. How an animal is affected by yet another model, chronic social defeat stress (CSDS), rather depends on context, rank, and sex. In this model a dominant animal is more affected by defeat than a (predisposed) subordinate one; the latter can predict outcomes and is better equipped to deal with a changing environment than the more rigid dominant animal. For instance, mouse lines genetically selected as'reactive' losers versus their'pro-active' aggressive congeners, show social withdrawal upon defeat. However, if dispersed in a novel environment, such "passive" animals are more resilient (reactive) than the dominant ones [246].

Active or passive coping styles were used as a criterion in tests on fear-motivated behavior (active and passive avoidance tests), learned helplessness test, SPBT, or the forced swim (FST) or variations thereof. The idea is that a passive coping response is the signature of a brain under chronic stress, while active coping would signal resilience. However, in these tests coping style is measured under different contexts. For instance, the SPBT provides an option to choose between passive and active coping; the fear avoidance and helplessness tests often measure passive behavior (freezing) as the only variable; while the FST allows recording of the transition from active escape to a passive immobile floating response.

To indicate the FST as a test or animal model of depression is an anthropomorphic qualification, simply because the acute response to the test condition is measured. Rather, by staying immobile the animal *optimizes* its chance for survival by saving energy resources. Furthermore, in the CSDS paradigm, attempts have been made to predict the outcome based on social avoidance, anxiety, and high CORT [205, 247]. Also, the extent of escape behavior in the first CSDS session predicts later outcomes, depending on the context [248]. Defeated mice are generally successful in avoiding harm; this is a trait, before and after CSDS [246, 249], and, accordingly, social hierarchy -and thus the outcome of CSDS can be established already in the home cage before CSDS testing [250].

with a hypersensitive GR. (Epi)genetic variation of FKBP5, an important modulator of MR and GR function associated with MDD risk [93, 94] (Box 2).

Summary of acute stress and clinical potential

Overall, the studies support the view that limbic MR is relevant for the tone, threshold, and sensitivity of the stress response system. Furthermore, the early phase of the stress response is dominated by hippocampal (limbic) MR-dependent pro-active appraisal and coping processes, i.e. risk assessment and memory retrieval. Moreover, MR activation drives a habitual response selection to *save* energy in the domain of social, emotional, and cognitive functions. If a stressor is appraised as a threat to integrity (depending on the state of the organism, see section 3), CORT secretion increases. GR becomes activated, initially via a non-genomic action involving endocannabinoids and together with MR. Subsequently, genomic actions take over to promote *costly* cognitive control, contextualization, and memory storage of the experience as well as recovery from the stressor. In this scenario, resilience is characterized by a rapid (MR-dependent) activation of CORT secretion combined with efficient (GR-dependent) termination (Fig. 3).

The studies in rodents, as well as findings in humans concerning MR or GR gene variants, suggest a specific role for MR and GR in psychopathology, which can be exploited in preventive or curative treatment of e.g. PTSD [95]. The time at which CORT receptors are manipulated is then of relevance. For instance, anti-glucocorticoids administered immediately after a traumatic event -the so-called golden hours- would interfere with *memory storage*, and thus would *prevent* the impact of trauma [96]. Alternatively, briefly before re-exposure, GR activation would interfere with *retrieval* of a previous traumatic experience and thus be helpful to attenuate symptoms [95, 97]. Anti-mineralocorticoids are also an option because of interference with the *retrieval* of fear-motivated behavior [98]. Finally, in a contextual fear paradigm, GR activation in the absence of the cue promotes *reconsolidation* of the experienced 'safety' and thus would facilitate *extinction* of the previously adverse experience [99–101].

ROLE OF TWO RECEPTORS IN CHRONIC STRESS

In rodent research, a variety of procedures have been applied to generate models for the study of the stress-diathesis theory underlying human affective disorders (Box 4). In this section, the

'chronic stress' construct is addressed and it is suggested how manipulation of MR and GR may help to reset such a dysregulated stress response system to restore adaptive coping.

The stressed brain in animal models of chronic stress

An earlier Expert Review [102] highlighted stress effects on the '*neuromatrix*', focusing on the transition of a 'healthy' to a 'stressed' brain connectome. This transition involves several (mutually interacting) phases.

Initially, a stress-induced phase of enhanced *susceptibility* is postulated, as an inroad to either a *resilient* coping style or transition to an apparent 'irreversible' chronic stress construct characterized by failed coping causing an increased *vulnerability*. Or as the late Bruce McEwen used to say: in such a case of crashed information processing "*the brain gets stuck*", meaning that the emotional brain remains in overdrive and behavior is dominated by habitual routines in an attempt to save energy while flexibility is lost [103]. This is allostasis at work, with excessive energy demand (allostatic load) in an attempt to keep emotions still at bay (Fig. 2).

Regardless of the chronic stress model used (Box 4), all procedures initially cause CORT hyperactivity. The ensuing hypercorticism refers to the flattened circadian rhythmicity caused in particular by elevated trough pulsatility, an enhanced CORT response to heterologous stressors, and downregulation of hippocampal GR mRNA expression. The stress response system has become sensitized by chronic stress and feedback regulation of CORT secretion occurs beyond the PVN-CRH/AVP neurons [104, 105]. This extrahypothalamic regulation of CORT secretion under chronic stress was confirmed in mutants where GR was exclusively deleted from the PVN [91]. Of note, while down-regulation of GR is common for chronic stress and MDD, another disease such as e.g. PTSD is characterized by increased GR expression and hypocortisolemia [7, 106–108].

The transition to a chronic stress construct is characterized by hypertrophy of the extended amygdala and orbital frontal cortex, while prelimbic (pl) and infralimbic (il) prefrontal cortex (PFC), and later also dorsolateral and ventral striatal regions, show retracted dendritic spines as a sign of atrophy and compromised mitochondrial functions [109–112]. The most prominent effects of chronic stress are found in the atrophy of the hippocampus. In imaging studies, the hippocampus appears smaller in depression and PTSD [113]. In rodents, the hippocampal dendritic tree shows clear signs of atrophy while neurogenesis is suppressed [109]. The Iba-1 expression in microglia is increased as a pro-inflammatory signature of neurodegenerative processes. MR supports this pro-inflammatory microglia activation [114].

When the brain circuits involved in cognitive aspects of coping and adaptation are atrophied due to chronic stress experience, the processing of a novel heterologous stressor will be entirely altered. This is exemplified by the profound transcriptional changes in the hippocampus and its subregions following an acute CORT injection or a stressor in chronically stressed rodents. In that case, inflammatory, epigenetic, and chromatin reorganization pathways that represent circuit degeneration become prominent, while pathways supporting neurogenesis and synaptic plasticity are suppressed [115, 116].

Circuitry

Using imaging methods in the human brain, evidence of the profound adaptive changes during chronic stress, PTSD and depression has also been shown. In a healthy brain, the perception and appraisal of a stressor initially activate a *salience* network. Then, over time when the stress response develops, rising CORT levels reallocate energy substrates by a GR-mediated action to the *executive* network which aims for cognitive control [26, 117–119]. In a recent systematic review and meta-analysis based on 31 fMRI studies. Berretz et al. [120], however, concluded that only the first salient network landmarks from perception and integration of sensory signals areas such as the insular cortex and claustrum provide a significant stress-induced change in BOLD signal.

Of great interest would be to know how acute stress affects connectivity between the salience and executive networks, since it may predict vulnerability precipitated by a chronic stress experience [121]. A recent study by the group of Karin Roelofs shed light on this. By examining police officers with above-average exposure to trauma, acute stress exposure enhanced activity of the salience rather than the executive network, while weakening connectivity to the default mode network. As the authors concluded: "*this study highlights the salience connectivity changes as a potential marker for trauma-related symptoms* [122]."

In rodents, pharmacological studies indicated that neuronal ensembles in plPFC, activated by a stress-induced locus coeruleus NE input, support coping aimed toward the source of the stressor by attacking, avoiding, escaping, or freezing arousal [123]. Using optogenetics, Ca^{2+} fiber photometry, and tract-tracing methodology this active coping style appeared to depend on a caudal/plPFC input to the dorsolateral periaqueductal gray (dlPAG) [124, 125]. The causal/plPFC also constrains physiological stress responses accompanying active coping, not only via this dlPAG hub but also by activating an excitatory projection targeting GABAergic neurons in the anteroventral BNST hub which controls the PVN-orchestrated neuroendocrine and sympathetic stress response [126–129].

How these circuits underlying stress-coping may shift to a chronic stress construct is beginning to be understood. One scenario is that a shift occurs from caudal/plPFC towards more rostral/ilPFC/dorsolateral striatum neuronal ensembles that govern habitual stimulus-response modes in coping [130, 131]. Another scenario refers to communication with the ventrolateral(vl)PAG to impose a passive coping response [125, 132]. A third scenario involves stress-induced impairment of a GR-mediated 'break' on the ilPFC excitatory efferent which as a consequence further enhances amygdala-based emotional arousal [133, 134]. In the coming years, knowledge of mPFC top-down control will rapidly increase.

Potential clinical relevance: reset of chronic stress signature with MR- and GR-antagonists

If animals are subjected to a chronic stress paradigm the daily application of the stressor generates a CORT response, which may decrease over time, as a sign of habituation to the daily stressor [109, 112]; this may eventually even result in hypocortisolemia. Interestingly, this decrease in the CORT peak can be prevented by daily pre-stress administration of an MR antagonist, an action that presumably involves a paraventricular thalamus hub [135, 136].

Carmen Sandi's team exploited the CORT profiles for the selection of animals that were exposed to an unpredictable repeated stress paradigm during puberty. Animals that failed to decrease their CORT peak (habituation) showed deficiency in the function of the MR-rich hippocampus, such as impaired spatial learning and memory [137]. Animals impaired in stress-induced CORT shut-off (impaired negative feedback) showed persistent GR-dependent emotional dysregulation and deficits in social competence. Interestingly, the latter deficits could be ameliorated by applying a GR-antagonist either at the time of peripubertal selection or at testing 8 weeks later, or even if administered out of the learning and memory context [138].

Other research also showed the potential clinical significance of GR-antagonists to reset symptoms of a dysregulated stress system [139]. Mifepristone can reverse e.g. stress- and CORT-suppressed hippocampal neurogenesis as well as synaptic plasticity [31] even within a few days [140–142]. Mifepristone and more selective analogs may correct metabolic disorder [143], cognitive decline, and tau pathology in models for Alzheimer's Disease [144] and

motor deficits in the Wobbler mouse, a model for amyotrophic lateral sclerosis [145]. In clinical studies, alcohol dependency in alcohol abuse disorder [146, 147] and psychotic depression [148], diseases involving high CORT, are also responsive to mifepristone and its more selective analogs. Interestingly, alcohol intake was also inhibited by the MR antagonist spironolactone; this may involve peripheral effects on osmotic balance. However, the strong effectiveness of GR-antagonists points to their potential use in reversing chronic stress-related disorders in humans too.

PROGRAMMING

Trauma or adverse experiences such as emotional neglect in early life are known to program the stress response system for increased susceptibility to later life stressors. One of the hallmarks of such a programming effect is an enduring change in HPA-axis activity and epigenetic modification of, notably, the GR. Fundamental for all early life studies in rodents is that i) these animals are born prematurely and ii) there is a stress hyporesponsive period (SHRP). During this SHRP the consequent low and stable circulating CORT concentration occupies predominantly MR; it is only after severe disruptions in mother-pup interaction that a brisk CORT response is additionally activating GR. Remarkably, such untimely activation of GR advances development as can be judged from e.g., earlier eye-opening but also cellular brain function. Here some representative findings are presented that have led to current concepts on early life programming of mental health and disease concerning CORT, MR, and GR.

CORT and its receptors in programming

"*Nothing is written in stone*" the late Seymour Levine used to say when referring to development as "*the laboratory of nature*." [149]. He discovered in rats that brief separations of mother and pup (handling) have lifelong consequences for stress responsivity and emotional behavior; this is because upon reunion the dam engages in vigorous nursing which attenuates stress responsivity for life [150]. In contrast, offspring of low-caring mothers show later in life more enhanced HPA-axis- and emotional reactivity than intensely nursed pups [151]. Neglected pups have, as adults, still atrophied hippocampal pyramidal neurons and epigenetically downregulated MR and GR expression, while contextual memory performance is impaired and neurogenesis suppressed [152]. These animals show increased social avoidance, but better performance in fear-motivated behavior as underscored by altered hippocampal and amygdala plasticity [153, 154]. Accordingly, experience in early life prepares for life ahead, as summarized in the match-mismatch or predictive adaptive capacity hypothesis [152, 155].

Many early life adversity models have been used. Systematic review and meta-analyses show that the licking-and-grooming (nursing) paradigm displays the largest effect size in later life outcomes [156] (https://osf.io/ra947/). This is of interest because most early life adversity animal models (e.g. maternal deprivation or limited bedding and nesting material) rely on the quality of maternal care and the pups' ability or opportunity to predict this [157]. The impact of care can be demonstrated during the 'SHRP'. If this period is disrupted by 24 h maternal deprivation, a hypothalamic CRH and pituitary ACTH response is evoked which can be readily normalized by stroking pups for 45 s every hour [158]. Interestingly, pups can adapt to short (up to 8 h of) daily deprivations: they quickly learn that the dam will return [159].

The abovementioned snapshot of studies fits into an 'interactive gene-environment-time framework' [160]. Time refers to the rate of maturation of the different brain circuits, from fertilization to the various stages of embryonic, fetal, and postnatal life, thus presenting at any moment a different substrate for processing environmental experiences. For instance, interference with mother-pup interactions during the first postnatal week typically affects amygdala and hippocampal functions; effects that can be normalized by brief treatment with GR-antagonists in early puberty [142, 161, 162]. Gene refers to gene variants, gene-environment correlations, and epigenetic modifications. Often such genetic influences also pertain to GR (and GR-associated) pathways. In a broader context studies in the past have led to the 'developmental origin of health and disease' (DOHAD) concept concerning the programming effects of undernutrition [163]. Regarding the programming of the brain and behavior, findings point to a U-shaped relationship between early experience and development of stress reactivity, and hence CORT response patterns. As stated: depending on genetic background, nature, and timing of the experience "*high-stress reactivity phenotypes disproportionately emerge within both highly stressful and highly protected early social environments*" [160].

Central in the programming of an anxious phenotype is the action of CORT in the early wake-up of the amygdala. This was demonstrated by Regina Sullivan and colleagues, using a paired odor-electric shock paradigm [164]. During the first week of life, pups display odor preference to secure attachment to the mother, even though the odor is paired with an electric shock. During the second postnatal week, on day 12 when animals exit the SHRP, exposure to the shock reverses odor-induced attraction into odor-induced fear-motivated avoidance. This switch from attraction to fear could be induced prematurely by the infusion of CORT in the amygdala. Conversely, ADX or mifepristone infused into the amygdala on day 12 maintained odor-induced attachment despite electric shock exposure [164, 165]. In other experiments, repeated daily separations during the first postnatal week also resulted in premature amygdala awakening, producing a later-life phenotype of social avoidance, increased emotional reactivity and memory, increased stereotypy, and impaired sensorimotor gating [166].

Potential clinical relevance of CORT and programming

In humans, evidence is growing that a similar CORT-depending switch is at the root of early amygdala awakening and, consequently, internalizing/anxiety problems. For instance, maternal depression and elevated CORT levels were found to be associated with increased volume c.q. connectivity of the 'right' amygdala, though only in female offspring [167–169]. Already at this early age 'fear' is programmed by amygdala lateralization of emotional information. These findings were supported by data from the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS) in Australia. Their results showed that maternal depression is associated with increased CORT reactivity in the offspring at 12 months of age; internalizing/anxiety problems occur at 4 years, but only in female offspring. Diminished placental 11-HSD-2 activity -allowing increased bio-availability of CORT- and epigenetic modification of the CORT receptors, seem to be at the root of this female-specific programming of an emotional 'amygdala' [170–173]. These studies suggest how early life trauma by activating a CORT-GR switch may program for life a vulnerable phenotype for anxiety disorders.

SEX DIFFERENCES

Most basic studies on the stress system have been performed with males. More recent research in rodents and man show that there are sex differences in stress-coping style that are reflected in HPA-axis activity, circulating CORT level, and MR-GR functioning.

Sex differences in the stress axis of rodents

Sex differences occur at all levels of HPA-axis organization, from limbic afferents to the PVN and its CRH and AVP secretion, and further downstream in pituitary ACTH release and CORT patterns. In rodents, females usually have higher stress-induced peak levels and duration of CORT secretion than males, also after GR deletion from PVN [91]. This difference is most pronounced at pro-estrus

when estrogen and progesterone levels peak. However, estrogens also enhance the synthesis of CORT-binding globulin, which increases the total pool of circulating CORT [174]. Accordingly, free circulating ultradian and circadian levels of CORT are identical across sexes, also in the brain [175]. Of note, progesterone is a ligand for the MR, acting as an antagonist of CORT [176]. Androgens suppress stress-induced HPA-axis activity, and like estrogens, their receptors are expressed in limbic structures [174, 177].

All of these factors might contribute to differences in stress-coping styles between the sexes. For instance, the preferred initial response of males to a threat is '*fight or flight*'. Coping of females, by contrast, seems to involve a more pro-social strategy, analogous to the human 'tend to befriend' [178–181]. Interestingly, icv administration of an MR antagonist or forebrain MR deletion impairs social discrimination and recognition in male but not in female mice [53, 182, 183]. CRISPR/Cas gene editing used to create a conditional GR knockdown in neurons of the plPFC, revealed sex differences in fear conditioning and passive coping [184].

For spatial learning, male rather than female rodents are impaired during acute and chronic stress [185]. The impaired performance of males appears to be compensated by an MR-dependent switch in coping strategy towards stimulus-response (habitual) behavior mediated by the dorsolateral striatum, at the cost of flexibility. Female mice show a switch in the opposite direction, particularly during estrous. Following forebrain MR deletion the switch in coping style is lost in both sexes [63, 183, 186].

The above sex differences in CORT secretion patterns and coping behavior may be caused by 'activational' actions of the sex steroids [187]. In addition, there are differences in 'organizational' actions of the sex steroids in early life that could be potentiated during puberty and may underlie the observed differences in coping style [188]. Sexual differentiation depends on the interaction between the X and Y chromosome and mitochondrial DNA that is inherited primarily via the mother. Accordingly, the Y chromosome Sry causes testis formation and testosterone-induced brain masculinization [188]. Transcriptomics of the sex chromosome complement revealed that immune and inflammatory genes expressed in microglia seem to bias the masculinization of the brain [189]. This finding opens up an additional role for CORT given its sexual dimorphic actions in the immune system and neuronal architecture [190, 191].

Potential clinical relevance of sex differences in stress

While the basal ultradian and circadian pattern of CORT does not differ between males and females [32], a sex difference in stress-induced ACTH and CORT secretion pattern is apparent in humans. Healthy men, when exposed to a Trier Social Stress Test (TSST), show higher ACTH and saliva CORT levels than women during all cycle phases of the cycle or contraceptive use [192, 193]. However, sex differences in CORT patterns need to take into account the difference in coping style between males and females; males may be more affected than females by the socio-evaluative threat and lack of controllability during the TSST. A systematic review and meta-analysis revealed that men suffering from MDD have a higher CORT peak response during exposure to the TSST than healthy controls, whereas the opposite direction was seen in women [194]. This difference disappeared upon remission.

PERSPECTIVES

Coping through MR and GR balance

In this expert review, we argue that MR- and GR-mediated actions are complementary in modulating information processing from stress perception and appraisal to coping and adaptation. By and large, MR activation modulates an *on-switch* involved in the selection of an appropriate coping response. The fact that i) MR implements FKBP5 in tuning GR-mediated control [195] and ii) also rapidly operates under stress with high CORT concentrations, adds to its importance in stress-coping [196]. These actions of CORT target in particular the hippocampus because of its rich MR expression. In fact, during development MR is a critical determinant of hippocampal molecular phenotype [53]. MR activation promotes dendritic spine turnover and enhances ciliary gene expression and neurogenesis while preventing neurodegeneration to support hippocampal function [43, 196, 197]. The *on-switch* by MR is permissive: by facilitating habitual responding, the cost of coping with stress is reduced.

In the acute stress response, GR-mediated actions operate the *off-switch* to prevent the initial defense reactions from overshooting and to promote energy expenditure for executive actions, recovery, memory storage, and long(er)-term adaptation. The responsivity to stress-induced CORT depends on the brain state, which is imposed in part by the hormone's circadian and ultradian rhythms. The latter allows CORT to be pro-active by enhancing perception and allocating metabolic energy in anticipation of stressors and upcoming daily activities, next to its reactive nature after stress [42, 45]. Since the stress response is turned on and off also during ADX (provided the electrolyte balance is maintained) one could argue that CORT action is not necessary. However, it is the *efficacy* of on/off switching of the stress response that is critical for resilience, and CORT is indispensable for this purpose.

MR-GR imbalance and chronic stress

Too much or too little CORT has damaging consequences for health because of the imbalance in MR-GR-mediated actions, a phenomenon represented by a U-shaped link between the CORT level and cellular or circuit activity [198, 199]. Neuronal vulnerability is highest at very low or very high CORT concentrations [9] and protection is best with a balanced receptor occupancy corresponding to the average daily circulating CORT concentration. MR-GR imbalance predisposed by genetic background, sex, and/or developmental epigenetic imprints due to DNA methylation, histone acetylation, and miRNAs, is at the root of disorders that can be characterized by GR resistance or hypersensitivity and HPA-axis dysregulation [200].

Chronically elevated CORT levels cause, via GR activation, hypertrophy of the central amygdala which is characterized by increased expression of CRH and enhanced emotional reactivity [109]. This amygdala hyperactivity occurs at the expense of atrophying mPFC, VTA, and hippocampal inputs to information processing, causing severe deficits in cognitive flexibility, reward processing, and contextualization [102, 109, 119, 201]. In the absence of additional (acute) challenges, this adaptive mode may perhaps suffice in coping with the situation at hand. However, heterologous stressors may reveal the vulnerability of 'the brain in chronic stress' and consequently, the adaptive potential (resilience) falls short.

The progression in this trajectory toward the 'chronic stress construct' is reminiscent of the three-stage cycle of the classical General Adaptation Syndrome: alarm, resistance, and exhaustion [5]. It also aligns with the attractive theory that the AVP/anxiety drive towards a *hyper*cortisolemic acute stress syndrome may be turned over time (years) to the *hypo*cortisolemic 'sickness' syndrome [7]. Another example of such a CORT-driven switch from a short-term beneficial to a long-term vulnerable state concerns the withdrawal/negative affect phase in addiction. Here, high GR and CRH expression go along with a negative emotional state due to an overactive central amygdala which is uncoupled from reward processing and cognitive control. Such a state is characteristic of many stress-related and metabolic disorders such as alcohol dependence, depression, PTSD, and obesity [202].

Interestingly, in alcohol-dependent animals, GR blockade in N.accumbens or central amygdala reduced alcohol consumption [146, 147]. Mifepristone is also effective clinically in the treatment of alcohol abuse disorder [203]. MR antagonist spironolactone too appeared to limit alcohol intake in animals and men via a mechanism that still needs to be defined precisely [204]. In the same vein, GR deletion (or mifepristone administration) in the N.accumbens part of the extended amygdala ameliorated the social aversion of defeated rodents [205].

MR and GR biomarkers in humans

The challenge is to compare the molecular and cellular findings of the MR-GR on/off switch during stress in animal models with resilience and vulnerability to psychiatric illness [12, 206]. For this purpose, as a proxy of the MR-GR switch in the brain, receptor function and genetics can be easily determined in circulating lymphocytes. This has revealed that carriers of the gain of function MR genetic variant are more readily inclined towards habitual responding under stress [66]. This MR polymorphism promotes optimism, protects against depression, dependent on sex and early life adversity [68, 70]. However, a functional epigenetic 'snapshot' of the brain still depends on the post-mortem status quo in particular circuits and cells [207, 208]. A novel approach is to train a model with machine learning, predicting MR-GR biosignatures at the single-cell level, but (clinical) validation remains necessary [209–211].

In this respect, Dex action appears to be very helpful as a surrogate for the endogenous role of GR in the containment of the stress reaction. It has helped the design of an epigenetic risk score for maternal depression and anxiety [207]. In a recent study, Starr-seq methodology was used to identify genetic variation in Dex-responsive transcriptional regulatory elements providing leads towards neurobehavioral traits characteristic for variations in GR resistance during stress responsivity and psychiatric disorders [212]. And so we are back at the value of a DexST as a window to the brain, but now with new approaches and evidence.

Towards MR- and GR-based treatment

For the potential treatment of stress-related disorders, it is essential to identify the defect in MR and GR functioning at the brain cell and circuit level. Quite apart from the poor accessibility of the brain, this is not trivial given the embedding of the receptor in different cellular contexts. This context -determining the eventual outcome- includes heat-shock proteins, co-chaperones, and cocktails of coregulators that link GREs with RNA polymerases at transcription initiation sites. Such coregulator cocktails show large differences between cells and tissues, which may explain why GR activation suppresses CRH mRNA in PVN, yet stimulates its expression in the amygdala [213]. The ligand-dependency of coregulator recruitment, however, also offers a unique opportunity for tissue-specific targeting of MR or GR with selective receptor modulators (GRM and MRM) [214–217].

The new findings with mifepristone demonstrate that 'reset', e.g. in particular brain areas, may be achieved by modulating GR activation. Although such a reset was demonstrated in the laboratory, its underlying mechanism is not completely understood [218, 219]. For progress, it would be desirable to obtain a local MR-GR biosignature of a disease condition as a sign of 'allostatic overload', which is many steps beyond the original DexST. Today such an allostatic load index is still based on (peripheral) blood levels of glucose, lipids, and a variety of stress mediators [220, 221]. Patterns of CORT secreted in blood or measured in saliva certainly provide information on setpoint, responsivity, and peak vs duration of the stress response, in support of an MR-GR biosignature. But -as with the DexST- it remains an incomplete window to the brain. The holy grail is to correct the deviant patterns in specific (brain and/or peripheral) tissues by MR-GR-like modulators targeting local receptor defects, which may be supported by lifestyle (mindfulness, exercise), psychotherapy, or additional pharmacotherapy [222, 223] to facilitate reset of the stress response system favorable for remission. To repair defects in local CORT action by novel receptor modulators would then provide Selye's personalized autopharmacology *'avant la lettre'*.

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ERdK and MJ contributed equally to conceptualizing and writing the manuscript.

COMPETING INTERESTS

ERdK owns stock of Corcept Therapeutics. MJ declares no conflict of interest.

ADDITIONAL INFORMATION

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