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Glucocorticoid hormone as regulator and readout of resilience☆

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The glucocorticoid hormones corticosterone and cortisol (CORT) are pleiotropic master regulators of resilience. This pleiotropy refers to the multifaceted CORT action in maintaining fitness and to promote stress-coping and adaptation. Mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) mediate this wide diversity of CORT actions complementary through rapid nongenomic and slower genomic mechanisms. The current contribution reports the following: i) brisk CORT reactivity and secretion patterns as hallmarks of resilience outcome, (ii) MR-mediated selection of coping styles and GR-mediated adaptation as a CORT-dependent switch in support of the resilience process, and (iii) the application of selective GR modulators to improve on resilience by attenuating inflammatory and emotional components of stress-related neurodegeneration. These findings highlight how CORT via MR and GR activation may modulate and monitor the resilience process and outcome in particular contexts.

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Introduction

Resilience is "*the process and outcome of successfully adapting to difficult or challenging life experiences, especially through mental, emotional, and behavioral flexibility and adjustment to external and internal demands*" [1]. This definition demonstrates that the multidimensional resilience and stress constructs are closely intertwined. The fact that the glucocorticoid hormones cortisol and corticosterone (CORT) — as end products of the hypothalamus-pituitary-adrenal (HPA)-axis — are pleiotropic master regulators of stress-coping and adaptation, intrinsically implies their importance in resilience.

CORT coordinates the sensation (or anticipation) and perception of a (psychological) stressor that triggers the rapid action of the central locus coeruleus noradrenergic (NA) and peripheral sympathetic nervous system (fight, flight, fright) and slower (re)appraisal processes. What is happening? Stop, look and listen. What can I do? Weigh the options, consult previous experiences by memory retrieval, exploit habits, or be creative [2]. CORT also coordinates the emotional, appraisal, and decision-making processes. The goal is to predict outcomes and gain control using an appropriate coping style to facilitate adaptation and restore homeostasis. CORT recruits and allocates the required energy to support defense reactions and drive emotions, an action critical for success in adaptation and, thus, for resilience. Finally, CORT integrates these functions over time in priming energy and immune functions and promoting memory storage to prepare for the future [3–6].

In the current contribution, we express our opinion on novel findings on CORT action in resilience in the context of an existing knowledge base of mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) function (Box 2). CORT is the principal ligand for the brain MR and GR, which mediate *slow* genomic actions; MR's affinity is 10-fold higher than that of GRs, implying that CORT occupies GR only after stress and at the circadian peak, while MR remains activated all the time. These facts are fundamental to the MR:GR balance hypothesis [6]. CORT also exerts rapid nongenomic effects via MR and GR in a broader concentration range; the affinity for these rapid nongenomic MR and GR is in the range of the slow genomic GR [7••]. The findings show that CORT (i) controls a switch in the resilience process via complementary MR- and GR-mediated actions, and (ii) its secretion patterns may serve as readouts for resilience outcomes.

☆ This article is dedicated to our colleague Dr. Fang Han (Box 1).

Box 1 In Memoriam

This article is dedicated to Fang Han, Ph.D., a distinguished young researcher from China Medical University in Shenyang City whose untimely demise is an immense loss. After her Ph.D. at Shenyang University, Dr. Han investigated the brain MR and GR at the laboratory of Professors Nishi and Kawata in Kyoto and with us in Leiden, the Netherlands. Our collaboration continued when Dr. Han rejoined Professor Shi's laboratory in Shenyang City. There, she specialized in studying of orexins and glucocorticoids at various levels of biological complexity in a rodent model for PTSD [75]. On June 27, 2024, Jinlang Ding, one of Dr. Han's students, successfully defended her thesis titled 'Glucocorticoid signaling in a rat model of post-traumatic stress disorder' at Leiden University.

Box 2 The brain MR.

The oxidase 11-hydroxysteroid dehydrogenase type 2 (11HSD-2) inactivates CORT in discrete neurons of the n tractus solitarii (NTS), as in epithelial cells in the kidney engaged in Na retention. This breakdown of CORT makes the MR aldosterone-selective, engaging these NTS neurons in salt appetite and cardiovascular regulation while innervating frontal brain regions involved in motivational, emotional, and cognitive processes underlying the maintenance of Na/K homeostasis. In most of the brain, the intracellular reductase (11HSD-1) regenerates CORT from its bio-inactive congener 11 dehydro-CORT. This brain MR is CORT-preferring because of its 100-fold excess over aldosterone; the receptor is promiscuous because it can bind aldosterone, progesterone, and deoxycorticosterone [76,77]. The intracellular MR (and GR) are nuclear receptors that regulate gene transcription. However, a fraction of the intracellular receptor is accessible at the membrane, mediating the nongenomic action of CORT [78]. CORT-MR primarily increases excitability in hippocampal and amygdala neurons (but decreases in mPFC), while CORT-GR has the opposite effect in these neurons. Hence, if the receptors are co-localized, a U-shaped dose-response curve occurs [79] (Figure 1).

Real-time ambulant measurement of CORT patterns

CORT circulates in a rhythmic pattern underlying the synchronization of daily- and sleep-related events. This circadian rhythm of CORT overarches an hourly ultradian rhythm of the hormone. Systemic or intracerebroventricular administration of antagonists to the high-affinity nuclear MR increases the basal am and pm levels and, thus, the setpoint of circulating CORT at any time of the day. The MR-dependent circadian trough is significant; if absent or reduced, the resulting flattened CORT rhythm compromises CORT responsivity, with consequences for resilience to stress-related disorders [6,8,9•].

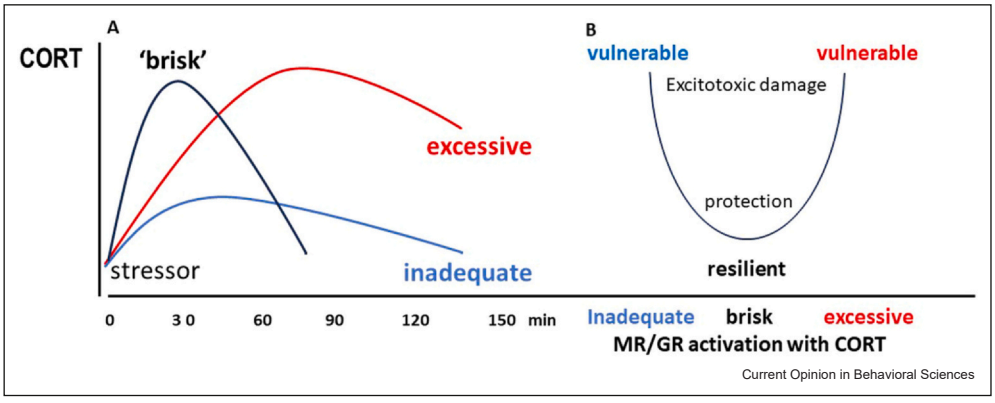
The rise in CORT concentration after stress initially activates rapid nongenomic processes mediated by the lower affinity membrane version of the MR concerned with attention, vigilance, fear, aggression, and selecting coping styles based on memory retrieval, appraisal outcome, and decision-making [10]. Thus, MR has two modes of action: firstly, nuclear MR is essential for the genomic tonic control of the stress response system; second, membrane-associated MR rapidly boosts the salient brain functions underlying the initial stress reaction [7••,11]. If MR is defunct, the initial stress reaction becomes dysregulated, compromising stress-coping and, thus, resilience.

Administration of an antagonist to the lower affinity GR increases the circadian/ultradian pulse amplitude with consequent deeper trough levels because high CORT levels occupy the lower affinity GR only in the morning (men) or evening (rodents) [12]. Rising CORT levels initially activate the GR nongenomic responses concerned with rapid endocannabinoid-mediated modulations of neurotransmission [7••]. High CORT further activates the genomic GR action to increase energy expenditure, promote emotional and motivational arousal, prevent overshoot of (immune) defense and HPA-axis reactions, and facilitate memory storage of the experience. Coping success and availability of energy substrates determine the collective outcome of all these GR-mediated actions that are fundamental for adaptation [11].

Failed coping includes a lack of cognitive control and uncertainty caused by the inability to predict the outcome of an action. The (re)appraisal processes continue, and the stress-induced HPA-axis, immune, and sympathetic activity persist. Accordingly, CORT feedback cannot overcome the hypothalamic corticotropin-releasing hormone (CRH)/vasopressin and pituitary adrenocorticotropic hormone (ACTH) drives, and the stress response duration persists. CORT is a metabolic hormone whose adrenocortical synthesis and target action depend on energy metabolism. Therefore, resilience becomes compromised if the circulating CORT response persists and energy expenditure exhausts. Or, in today's terminology, the process of adaptation is called allostasis and its cost, allostatic load [3,13].

Criteria for judging this allostatic load are the shape of the basal ultradian and stress-induced patterns of circulating total CORT or, in saliva, the free fraction of CORT not bound to corticosteroid-binding globulin. In this respect, the onset of the CORT response depends on the central drive to the HPA axis and the bioavailability of energy substrates to synthesize the hormone. The duration of the CORT response reflects the success of stress-coping and adaptation. Accordingly, rapid response to an acute stressor is a sign of resilience, but only if the duration of CORT secretion turns off efficiently [6,14] (Figure 1).

Figure 1



CORT as readout and regulator of resilience. **(a)** CORT reactivity as read out. Successful coping with an acute stressor is characterized by a rapid onset and efficient termination of CORT secretion, which is considered to support resilience (brisk). If coping fails, the CORT reaction may become excessive and prolonged because of feedback resistance, resilience is compromised, and vulnerability is enhanced (excessive). Vulnerability is also increased if CORT reactivity is reduced and inadequate to support defense reactions and metabolism (inadequate) [3,6,70]. **(b)** CORT as the regulator. Neurophysiological studies have revealed a U-shaped dose response as a function of the MR/GR occupation ratio. Moderate exposure to CORT leading to predominant MR occupancy is important for neuroprotection, and additional GR occupation (for a limited period) results in attenuation of increased local excitability. Too low (little receptor occupancy) and too high CORT exposure (excess MR and GR occupancy) increase the vulnerability of neurons because of excessive transmitter responses and excitotoxicity [6,79,81]. For the most recent update on how (non)genomic MR- and GR-mediated actions control neuronal communication, see Ref. [7••].

Recently, an ambulatory microdialysis system became applicable in humans, which permits continuous 24-hour sampling of CORT from subcutaneous fat tissue. Stafford Lightman's laboratory applied the microdialysis system with a liquid-chromatography tandem mass spectrometry, which could simultaneously measure more than 50 adrenal steroids [15••]. This real-time adrenal 'corticosteroidome' collected under ambulant conditions currently provides the most informative marker for examining CORT patterns as an index for the resilience process and outcomes. The real-time ambulatory assessment of free CORT heralds a new chapter in clinical endocrinology. It will be possible to better understand variations in the CORT patterns under normal and disease conditions in males and females during development, adulthood and aging [9•].

The new technology may assist in the further validation of the finding that 'concordance' of stress-induced CORT and sympathetic reactivity with the experience and behavioral expression of 'stress' is a sign of resilience that protects against depression. This person-centered multisystem approach can detect a mismatch in stress-induced CORT reactivity patterns vs experience/expression-related stress response features [16,17••]. Such a mismatch (dis-concordance) may be of genetic origin and programmed by (early) life experience and is a significant factor in compromising resilience [18].

The following two sections will focus on the role of CORT in cognitive control, coping, and adaptation underlying the resilience process. The final section focuses on the potential of novel GR modulators in rescuing resilience. A detailed analysis of the mitochondrial, molecular, and cellular underpinning of these complementary MR- and GR-mediated actions is beyond the current scope, and we refer the reader to recent outstanding publications [4,7••,19,20••].

CORT and cognitive control

But how does CORT action contribute to the resilience process in the brain? For further understanding, this section will focus on the pathways underlying the processing of a stressor. Physical stressors (infection, tissue damage, pain, blood loss, and metabolic imbalance) activate the paraventricular nucleus (PVN) and HPA axis via ascending neural pathways. In contrast, psychological stressors require processing via multisynaptic pathways in the limbic forebrain. The expression of c-fos marks the multisynaptic pathways induced by stress that underlie processing and converge on the PVN [21].

In the hippocampus, c-fos staining identified a sparsely distributed network of GR-responsive neurons that harbors a memory engram in contextual behavioral paradigms [22,23•]. Lesuis et al. [23•] discovered that CORT administered after fear conditioning induced a generalized fear response accompanied by increased activity of this sparse GR-responsive dentate neuronal network. Chemogenetic suppression of the activated dentate neurons, and thus of GR function, restored the contextual fear response.

Another recent study showed that generalization of the fear response also occurs by activating the GR in the lateral wings of the dorsal raphe serotonergic (5HT) neurons. Local viral GR knockdown or GR antagonist treatment of the animals reinstated the original contextual fear conditioning. Strikingly, the mechanism underlying fear generalization seems to be CORT-GR control of a switch in the neurotransmitter phenotype of these 5HT neurons from glutamatergic to GABA-ergic, as judged by the change in VGLUt3 to GAD67 expression [24••]. The 5HT neurons innervate the central amygdala, lateral hypothalamus, medial prefrontal cortex (mPFC) [25], and hippocampus, suggesting that a CORT-GR switch from Glu to GABA in this circuit underlies the transition to fear generalization as a model for anxiety disorders. Indeed, a similar shift in transmitter phenotype was observed in the post-mortem human brain of post-traumatic stress disorder (PTSD) patients [24••].

The central amygdala can activate the HPA axis, the locus coeruleus NA network, and the sympathetic nervous system [26]. CORT induces CRH mRNA expression in the central amygdala to increase the capacity to respond to threats with fear and aggression in the context of this physiological stress response [27]. While the central amygdala gates fear responses, the nearby basolateral amygdala (BLA) processes its modulations triggered by sensory information [28]. For this purpose, nongenomically, CORT synergizes with NA in the BLA. CORT's action depends on these neurons' recent history, a phenomenon called synaptic metaplasticity. Thus, with low concentrations of the NA agonist isoproterenol, subsequent CORT activation inhibits the transient excitation. In contrast, with high concentrations of the stress hormone mimicking severe stress, the glutamatergic activation of BLA neurons is enhanced [29]. The BLA communicates this information bi-directionally with the mPFC, hippocampus and the n. accumbens [7••,11,28].

The medial mPFC controls emotions such as fear generated by the amygdala, the ventral striatal-based reward processing and motivation, decision-making, and working memory, among many other functions. Control of coping style also belongs to the mPFC portfolio; rostral to caudal divisions of the prelimbic and infralimbic neuronal ensembles (also called ventromedial and dorsomedial PFC, respectively) harbor a variety of functions underlying coping with acute and chronic stress. Thus, while management of acute stress links mainly to prelimbic ensembles, CORT is instrumental during chronic stress in inhibitory control of the infralimbic PFC over amygdala function and HPA-axis activity [25,30].

Jason Radley's lab applied optogenetic techniques and track tracing combined with Ca2+ imaging in a series of studies to examine how mPFC-based cognitive control and CORT are linked. Their latest study aligns with the classic findings on dorsolateral periaqueductal gray (PAG)-linked sympathoexcitation/active coping and ventrolateral PAG-linked sympathoinhibition/passive coping [31]. Their findings added three layers of complexity: (i) Ca 2+ imaging revealed that the caudal prelimbic PFC and dorsolateral PAG pathway activity correlated with active coping in the so-called shock-prod burying test (SPBT) which is a method used to assess coping mechanisms in response to stress. (ii) optogenetic activation of this pathway causally enhanced active coping, and (iii) prelimbic PFC-dorsolateral PAG activation counteracts the reduction in active coping produced by an additional acute stressor (i.e. removal of the bedding in the SBPT) or by a history of chronic stress. Notably, the switch to an active coping style suppressed the peak rather than the duration of CORT secretion [32,33••].

The findings suggest that top-down cognitive control by the mPFC is downstream ultimately via the PAG, expressed in coordinated behavioral and physiological responses to promote coping and adaptation. For this purpose, the mPFC-based cognitive control must coordinate the CORT-driven emotional and motivational drives with stress-coping and adaptation. Such an integration becomes apparent from studies with genetically selected and/or engineered animals, which associate extreme differences in coping styles and cognitive control with CORT patterns, sympathetic responsivity, and hippocampal MR expression [34–36].

CORT and coping style

Spatial learning, fear conditioning, and social interaction paradigms demonstrate in rodents that MR activation determines the shift from hippocampal-based contextual to a less costly habit learning directed by what appears to be a striatal mechanism. This switch may circumvent the deterioration of performance that the original contextual strategy suffers from, particularly during chronic stress. In men, using the probabilistic classification learning task with simultaneous functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) also showed that cognitive performance switched to habitual behavior following stress while increasing the amygdala-striatum at the expense of amygdala-hippocampal connectivity [11,37].

In line with a role for MR, stress facilitated habitual learning in males and females carrying the 'haplotype 2' MR gene variant (rs2070951 and rs5522; frequency of ~0.38) that encodes an MR with increased bioactivity *in vitro* [38]. Previous studies demonstrated that MR-haplotype 2 was

associated with increased dispositional optimism, less feelings of hopelessness and rumination, and increased resilience to depression in females [39]. Another study with school teachers showed an association between MR-haplotype 2 and coping with perceived chronic stress; this MR gene variant enhanced CORT, ACTH, and heart rate responses to the Trier Social Stress Test (TSST) [40]. MR-haplotype 2 also attenuated the negative influence of childhood maltreatment and enhanced prosocial behavior, empathic concern, and perspective-taking, which protect against depression, particularly in women [41].

McCann et al. and Oakley et al. discovered that MR is a terminal selector transcription factor determining the molecular phenotype of the hippocampal CA2 pyramidal neurons [42••,43]. The loss of identity included the RSG14 protein, which regulates Ca sequestering in dendritic spines underlying long-term depression and plasticity resistance. The CA2 neurons and other hippocampal regions are vasopressin/oxytocin receptor hotspots targeted by a neuronal network underlying 'sociability' and cognitive functions originating from the hypothalamic submammillary nucleus. The discovery highlights the hippocampal MR as a locus of social and spatial encoding/learning and memory retrieval. There are sex differences. Females lacking hippocampal MR or both MR and GR used more anxiety-like behavior and active stress-coping styles, while in the male mutants, cue-dependent fear-motivated learning prevailed. Moreover, the MR mutants showed decreased sociability only in males [44••].

Oakley et al. [43] noted that hippocampal MR deletion (at postnatal day 9) from hippocampal neurons caused neuronal degeneration of the dentate gyrus. This phenomenon also occurs after adrenalectomy (ADX), where CORT and aldosterone replacement suppress apoptosis and reinstate neuronal birth [45]. Previous research showed that MR regulates 5HT1A receptor expression [46], while the typical GR-responsive L-type calcium current was absent [47].

Transcriptome analyses of the MR mutants showed a matching profile between males and females of deleted MR-responsive genes but with a differential expression more extensive in females [44••]. Using genome binding as a criterion revealed a particular enrichment of MR-responsive genes involved in neuronal differentiation and ciliogenesis in the hippocampus [48]. Upon MR gene deletion of the forebrain, an inventory was made of MR target genes [49], including FKBP5, which regulates in an ultra-short feedback loop MR and GR activity [50].

The findings underscore that the hippocampal trisynaptic network, particularly the CA2 and dentate gyrus, is primarily an MR target — functions like contextualization and sociability link to hippocampal MR activation in a sex-dependent manner [51]. MR activation is necessary for selecting coping styles, and its genetic variants sex-dependently modulate resilience to depression.

CORT receptor antagonists promote recovery of resilience

CORT-induced hippocampal degenerative processes in rodent models of chronic stress are well-documented. Alternatively, there are also animal models ofneurodegenerative disorders that demonstrate aspects of stress-induced changes and hypercortisolism. A striking common denominator in all these disease models is that the mixed GR/progesterone antagonist mifepristone restores signs of degenerated (excitotoxicity, atrophy, and impaired dentate neurogenesis) hippocampal function ([52,53]. But how does it work?

Meyer et al. [54•] showed that the GR antagonist CORT 113176 (Dazucorilant) (Box 3) normalized the increased circulating CORT and ILß in a male chronic stress mouse model. Dazucorilant decreased mRNA and immunohistochemical markers of the spinal cord stress-induced Iba1+ microgliosis, GFAP+ astrogliosis (including water-channel Aquaporin4), and the pro-inflammatory cascade from alarmin (HMGB1) via increased TLR4, MyD88, and Nuclear Factor kappa-light-chain-enhancer of activated B cell (NFκB) expression towards enhanced NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome function. Dazucorilant and mifepristone also suppressed these signs of inflammation in several animal models of neurodegenerative diseases and improved functional deficits. These include, for example, the mouse model for Alzheimer's disease, amyotrophic lateral sclerosis

Box 3 Selective CORT receptor modulators.

The classical way to attenuate GR signaling at the level of the receptor is with mifepristone/RU486. However, cross-reactivity with the progesterone receptor and strong disinhibition of the HPA axis are clear disadvantages. A selective GR antagonist, Relacorilant, is currently in phase 3 clinical trials for Cushing's disease and oncology indications (GRACE, GRADIENT, and ROSELLA trials). Strikingly, this antagonist shows much less disinhibition of the HPA axis [59,60]. This difference in functional consequence of GR blocking suggests that these ligands differentially affect the molecular signaling of GR, e.g., at the level of transcriptional regulation. This increased selectivity indicates 'receptor modulation' rather than passive antagonism. These selective GR ligands, such as Dazucorilant, are clinically evaluated for the treatment of ALS (DAZALS trial). Recently a selective GR degrader was developed that enables rapid reversible GR depletion as an alternative to GR antagonists or GR modulators [80].

(ALS), Huntington's disease, and Type 1 diabetes [55–58]. Hypercorticosteronism is a common characteristic of all these rodent models. However, GR antagonist treatment does not always normalize HPA axis activity, which argues for a direct beneficial consequence of antagonism at the GR rather than a reduction of CORT, but see Ref. [59,60]

One explanation of the efficacy of the GR antagonists is that they interfere with the priming of innate immunity by excess CORT. The priming of innate immune function occurs in activated microglia, as is demonstrated in the above models. However, the action of the GR antagonists is rapid, while the signs of inflammation slowly develop over days and weeks in the disease models [57,61,62]. Therefore, rapid disinhibition of a clearance mechanism such as the 'glymphatic' flow could also be an explanation. This reasoning implies that excess CORT inhibits the rate-limiting gene Aquaporin 4 in astrocytes, as was shown recently. However, the GR antagonists reduced the hypertrophied astrocytes and increased Aquaporin 4 expression in the chronic stress model, arguing against the glymphatic system's role [63].

While the previous paragraphs highlighted the reinstatement of resilience by GR antagonism, other research shows that MR's blockade can also be effective because MR activation is proinflammatory and prosympathetic. For instance, previously, CORT-MR gene deletion in myeloid cells limits ischemic brain damage by restricting the proinflammatory macrophage/microglia response [64]. The de Nicola/Garay et al. laboratory showed that a high dose of the MR antagonist eplerenone was effective in a mouse model for experimental autoimmune encephalomyelitis generated by the administration of Myelin Oligodendrocyte Glycoprotein (MOG35–55). Eplenerone given in high doses to penetrate the blood–brain barrier improved clinical signs and prevented demyelination in the spinal cord [65]. MR blockade is efficacious in damage control in models of hypertension with MR overexpression, either of genetic origin in the spontaneous hypertension rat (SHR) or in the traditional deoxycorticosterone acetate (DOCA)-salt model [66].

The latter findings are reminiscent of the Oakley/Cidlowski discovery [67], using selective MR, GR, or combined MR–GR gene deletion in mouse cardiomyocytes. These studies led to the conclusion that enhanced MR activation may compromise a GR-controlled cardioprotective mechanism by causing cardiac hypertrophy and left ventricular systolic dysfunction, leading eventually to cardiac failure. The authors concluded that 'balanced cardiomyocyte MR- and GR-mediated signaling' is crucial for cardiovascular health, arguing why MR antagonists are effective against cardiac remodeling. MR antagonists interfere with the proinflammatory cascade activated by tissue damage that produces myeloid cells.

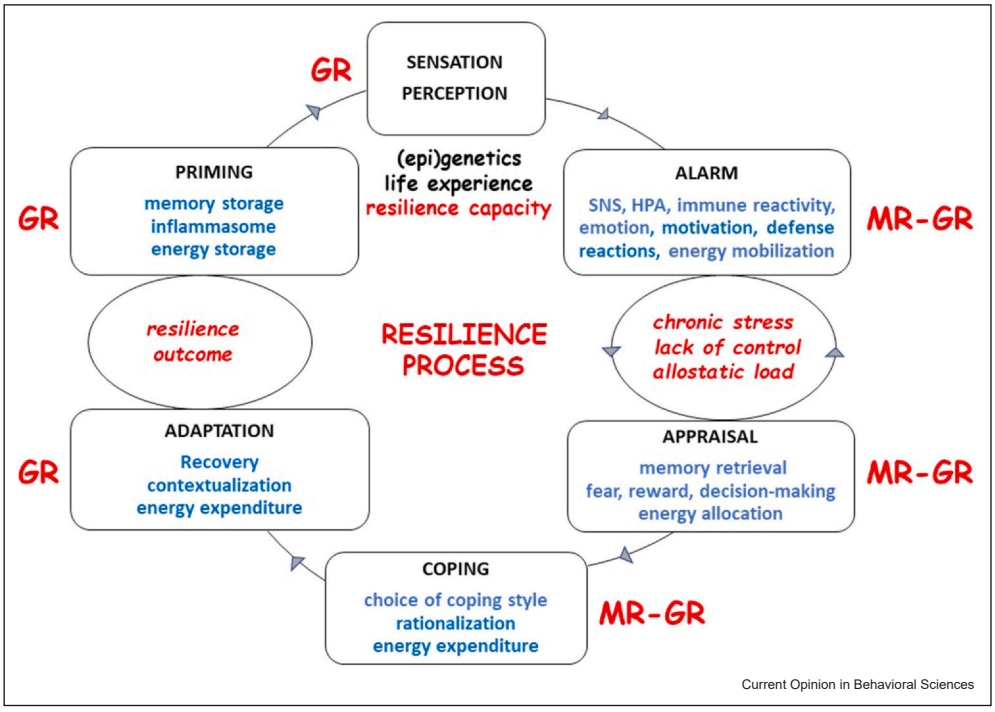
Clinically, MR antagonism is a lifesaver in heart disease and protective in stroke models, thus mostly linked to cardiac functions, endothelial cell damage, and regenerating myeloid cells. This beneficial action of the MR antagonist occurs in a proinflammatory context triggered by tissue damage, mineralocorticoid overexposure, or MR overexpression. GR antagonism is valid for treating generalized hypercortisolism and excess GR functionality, as seen during Cushing [68]. The new class of selective GR modulators (SGRM) allows the discrimination between defense reactions, emotional drive, and energy metabolism. Preclinical and clinical studies include a wide range of disease areas such as metabolic disease (MASH), oncology, depression/PTSD, and neurodegenetive disorders, i.e. ALS, but it is not possible at this stage to accurately predict which disease will benefit from which SGRM.

Concluding remarks

The current contribution focused on four novel developments in the science of resilience. Firstly, the real-time ambulatory measurement of bioavailable CORT patterns to assess resilience outcomes, preferably by simultaneous monitoring concordance with the stress experience. Secondly, the optogenetic manipulation of the limbic-forebrain circuitry to examine the mPFC cognitive control over GR-driven emotions underlying the resilience process. Thirdly, the study of the brain (hippocampal/amygdala) MR function underlying sex-dependent stress-coping styles and, thus, the core of resilience. Finally, the rapid reversal of compromised resilience by GR antagonists in animal models of chronic stress and neurodegeneration is promising for clinical practice.

The fundamental idea behind our viewpoint is that the activation of MR and GR plays a complementary role in mediating cortisol's effects on stress coping and adaptation, which are central to the process of resilience.: the MR:GR balance hypothesis. MR-mediated actions are concerned primarily with the initial alarm, memory retrieval, and appraisal phase of the stress response, leading to sex-dependent coping styles. The later GR activation provides the necessary energy, prevents MR-stimulated defense reactions from overshooting, and promotes contextual memory formation, NLRP3 inflammasome building, and energy storage to prepare for future stress-coping as part of the adaptation program (Figure 2) [69].

Figure 2



CORT and Resilience: The resilience process, initiated by the actual experience or anticipation of a stressor, begins with the sensation and perception through alarm and appraisal mechanisms, leading to coping, adaptation, and preparation for future similar challenges. This preparation involves storing the memory of the experience, forming an NLRP3 inflammasome in the innate immune system, and accumulating readily available energy substrates. Combined with genetic predisposition and epigenetic modifications from early life experiences, this builds the organism's capacity for resilience. Chronic stress, however, can lead to a bottleneck in information processing, leaving the brain 'stuck' in a state of uncertainty and lack of control, undermining the resilience process. This is evidenced by disrupted circadian rhythms and prolonged or inadequate stress-induced CORT secretion. The non-genomic and genomic actions of CORT, represented by MR and GR receptors, must be synchronized and balanced for optimal resilience, as proposed by the MR:GR balance hypothesis.
Adapted from Ref. [82].

Failure to cope causes a chronic stress condition characterized by elevated and prolonged CORT secretion, resistance to GR-mediated feedback action on defense reactions, HPA axis overactivation, sympathetic overactivity, and enhanced emotional drives. This condition compromises resilience and increases vulnerability to stress-related brain, metabolic and immune diseases. Agorastos and Chrousos labeled this state 'acute stress syndrome' [70].

This acute stress syndrome may change over time into a 'sickness syndrome' characterized by exhausted energy resources, impaired mitochondrial functions, and a hyperphagic, proinflammatory phenotype [70–73]. Circulating CORT levels become low as if the energy is lacking for mitochondrial synthesis and action of CORT. Fibromyalgia, chronic fatigue syndrome, and atypical depression are its clinical manifestations. It is a reminder of Selye's General Adaptation Syndrome, where a phase of resistance precedes exhaustion or, in today's language, allostatic overload [3,70].

A recent integrated multi-omics study of post-mortem mPFC, central amygdala, and hippocampal dentate gyrus tissue supports the critical role of CORT and inflammation in stress-related brain disorders. Integrated transcriptomic, methylomic, and proteomic data pointed to IL1B, GR, STAT3, and Tumor Necrosis Factore (TNF) as top stream regulators in the vulnerability and pathogenesis of major depression and posttraumatic stress disorder [20]. This discovery supports the notion that tissue-specific GR modulators may rescue the compromised resilience process by modulating the underlying overactivity of GR in stress and defense mechanisms.

Finally, studies on resilience to stress unfortunately have various designs and relatively low statistical power, and they will benefit from using historical data. Worldwide data-sharing and collaborative interdisciplinary initiatives have begun to combine (neuro)biological, physiological, and behavioral data across many acute stress studies to meet this concern. These initiatives include

the 'STRESS-NL database' (www.stressdatabase.eu) [74] and the Global Stress and Resilience Network (GSRN) (https://www.stressnetwork.ch), which is led by Dominique de Quervain and Carmen Sandi.

Declaration of Competing Interest

Onno C. Meijer receives funding from Corcept Therapeutics, USA , which develops GR modulators for clinical use.

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