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Chapter

MR/GR Signaling in the Brain during the Stress Response

Edo R. de Kloet and Onno C. Meijer

Abstract

This contribution is about mineralocorticoid receptors (MRs) in their capacity as mediators of glucocorticoid action in the brain. This paradox has evolved because MRs are promiscuous and bind with high-affinity cortisol and corticosterone as well as aldosterone, deoxycorticosterone, and progesterone. The MRs "see," however, predominantly glucocorticoids, because of their 100–1000-fold excess over aldosterone; bioavailability is further enhanced because of local regeneration of glucocorticoids by 11βOH-steroid dehydrogenase (HSD-1). In contrast to these *glucocorticoid-preferring* MR, the evolutionary later appearance of *aldosterone-selective* MR in epithelial cells depends on co-localization with the oxidase 11β-hydroxysteroid-dehydrogenase type 2 (HSD-2) in a few hundred neurons in the nucleus tractus solitarii (NTS), which innervate frontal brain regions to regulate cognitive, emotional, and motivational aspects of salt appetite. The glucocorticoid-MRs and classical glucocorticoid receptors (GRs) mediate in a complementary manner the glucocorticoid coordination of circadian events and mediate the regulation of stress coping and adaptation. If an individual is exposed to a threat, MRs are crucial for the selection of a particular coping style, which is via GR activation subsequently stored in the memory for future use. Our contribution is concluded with the notion that an imbalance in MR- and GR-mediated actions increases susceptibility to stress-related disorders.

Keywords: stress, brain, behavior, inflammation, glucocorticoid receptors, mineralocorticoid receptors

1. Introduction

The naturally occurring glucocorticoids, cortisol and corticosterone (the latter only in rodents), are secreted as end products of the hypothalamus-pituitary-adrenal (HPA) axis. The glucocorticoids have two modes of operation. Firstly, the hormones synchronize and coordinate circadian and sleep-related events. This action is based on hourly ultradian pulses with increasing amplitude toward the start of the active period with the goal to generate the necessary energy for the day to come. The hourly pulses maintain responsivity to the glucocorticoids. The frequency and amplitude of the glucocorticoid pulses may change as is the case during, e.g., inflammatory disorders and depression, or may become irregular as part of the aging process. High glucocorticoid concentrations prevent the onset of sleep [1–3].

Secondly, the glucocorticoids mediate the response to stress. A "stress reaction" can be due to physical stimuli such as pain, blood loss, and infection or can be psychogenic. Anticipation is an important component of the psychogenic stress reaction. Hence, the prediction of an upcoming event and the ability to exert

control are essential for effective coping irrespective whether it concerns an adverse experience or a reward. Actually, stress is the "spice of life" and essential for adaptation and survival. However, the most severe stressor is characterized by inability to predict upcoming events and uncertainty during a threat. If uncertainty because of lack of control persists, the very same glucocorticoids that promote adaptation are now disruptive, facilitate breakdown of adaptation, reduce resilience, and enhance vulnerability to disease [4].

Glucocorticoid secretion from the adrenocortical zona fasciculata is under the control of pituitary adrenocorticotropic hormone (ACTH) that is cleaved from the large precursor molecule: pro-opiomelanocortin (POMC). The anterior pituitary synthesis of POMC is driven by corticotropin-releasing hormone (CRH) from neurosecretory cells of the paraventricular nucleus (PVN) in the hypothalamus; co-localized vasopressin amplifies the CRH-induced release of ACTH. Physical stressors directly activate CRH neurons via ascending neuronal projections of the brain stem. Psychological stressors are processed in higher brain regions for appraisal, decision-making, and choice of coping style to deal with the stressor. At last, the stress reaction dissipates and the experience is stored in the memory [5].

2. Corticosteroid receptors

The action of glucocorticoids is mediated by two types of corticosteroid receptors. One type is, surprisingly, the mineralocorticoid receptor (MR). This receptor was first identified in 1968 by Bruce McEwen: retention of ^{3}H-labeled corticosterone was observed in hippocampal neurons at 1 hour after administration of the tracer to an adrenalectomized (ADX) rat [6]. ^{3}H-aldosterone given to ADX animals showed essentially the same neuroanatomical distribution pattern as ^{3}H-corticosterone. The MR was cloned: immunoreactive (ir) MR protein and MR gene expression showed the same distribution pattern as radioligand binding in the hippocampus [7, 8].

The GR was initially not detected by in vivo radioligand binding studies for two reasons. Firstly, the amount of radiolabeled corticosterone tracer was insufficient to occupy GR, because this receptor binds cortisol and corticosterone with a tenfold lower-affinity than the high-affinity MR. Second, our in vivo tracer studies with the high-affinity GR ligand, dexamethasone, did not provide a signal in the brain because the synthetic steroid was exported by multidrug resistance P-glycoprotein localized in the blood-brain barrier. When pure glucocorticoids became available, we managed to identify distinct populations of MR and GR in vitro. GR was found widely distributed in the brain and highly expressed in the typical stress centers. MR and GR are abundant and co-localized in limbic neurons [9, 10].

The MRs actually occur as glucocorticoid-preferring and aldosterone-selective variations in receptor function. Aldosterone-selectivity occurs solely in epithelial cells engaged in Na homeostasis. In a collaborative study with Edwards et al., we discovered in 1988 that aldosterone selectivity hinges on co-expression with the enzyme 11β-hydroxysteroid-dehydrogenase type 2 (HSD-2), which breaks down the naturally occurring glucocorticoids, cortisol and corticosterone, into their inactive 11-dehydro congeners [11]. The Australian group led by John Funder reached the same conclusion [12]. In the brain, the *aldosterone-selective* MRs involved in salt homeostasis are mostly restricted to neurons of the nucleus tractus solitarii (NTS) and the circumventricular organs. The MR-NTS neurons project to limbic forebrain regions, notably the locus coeruleus area involved in arousal and the bed nucleus of the stria terminalis (BNST). Via the BNST hub, the NTS neurons can affect emotions, memory performance, and reward processing [13–15].

A pharmacological amount of aldosterone, administered to rats, is anxiogenic and causes changes in coping with stress [16]. Such an effect can be explained by overstimulation of the aldosterone-responsive brain network. In fact, patients suffering from essential hypertension have an enhanced aldosterone secretion following stress exposure [17]. It would be of interest, therefore, to further explore this line of research, particularly in light of the persistent evidence of excess mineralocorticoids and aberrant MRs as risk factors for mood disorders [18, 19], also in patients with Conn's syndrome [20]. In addition, the brain aldosterone MRs were found to be causal in hypertension in case a high-salt diet was offered [21], see overview on aldosterone and mineralocorticoid receptors [22].

The majority of MRs that are abundantly expressed in limbic-frontocortical neurons were identified as *glucocorticoid-preferring*. This is because cortisol and corticosterone are present in a 100–1000-fold excess over aldosterone, thus competing out aldosterone binding, even though part of the circulating glucocorticoid is bound to corticosteroid-binding globulin (CBG). Accordingly, these glucocorticoid-preferring MRs predominantly "see" the naturally occurring glucocorticoids, cortisol and corticosterone. Moreover, glucocorticoid preference is further enhanced by co-expression with HSD-1, which regenerates locally bioactive glucocorticoids from the inactive 11-dehydro congener [23]. Finally, MRs are promiscuous in that they bind in addition to glucocorticoids and aldosterone also progesterone and deoxycorticosterone. This promiscuity may be related to the fact that evolutionary the MRs preceded the GRs, progesterone receptors and androgen receptors [24].

Thus, some 30 years ago, we felt as if we were "digging gold." We knew the precise localization of MR and GR in the brain and that these receptors did bind the same hormones—cortisol and corticosterone—but with an order of a magnitude difference in affinity. This was the start of a systematic search for their molecular, cellular, neuroendocrine, and behavioral function, together with the group of Marian Joëls in Amsterdam. This helped to define better the temporal, spatial, and contextual domains of the stress response that are so extremely important for understanding stress coping and adaptation [25–28]. Before discussing MR/GR function, we will first briefly summarize the main aspects of their role in the molecular and cellular mechanisms of glucocorticoids.

3. Molecular mechanisms of MR-/GR-mediated actions

The non-genomic effects notwithstanding (see Section 4) MR and GR are best understood as transcription factors involved in the regulation of gene expression. Classically, their differential effects have been related to (besides cell-specific expression) transcriptional effects that are independent of the highly homologous DNA-binding domain. For example, an important part of the anti-inflammatory actions of GR activation depends on interactions of GR monomers with pro-inflammatory transcription factors such as the "nuclear factor kappa-light-chain-enhancer of activated B cells" (NF-κB), a process called transrepression, and these interactions are much weaker for MR [29]. Recently, the interaction of the GR monomer with NF-κB was challenged with the discovery of GR binding to "cryptic" DNA sequences within the genomic NF-κB response elements (κBREs) that mediate GR-driven repression of inflammatory gene expression [30].

Recent studies that evaluated MR and GR binding to the DNA in the hippocampus indicate that the receptors interact with the DNA via their—homologous—DNA-binding domains [31–33]. MR and GR share 96% homology in their DNA-binding domain, and both recognize the same "GRE" sequence in the DNA to

which they bind as homo- or heterodimers. Yet, they differ in other parts of the protein, in particular in their large N-terminal domain. The best known target genes that are shared between MR and GR are *FKBP5*, *Sgk1*, *GILZ*, and *PER1*. For these genes, GR activation seems to extend the MR-mediated action by an order of magnitude, as shown in dose-response studies.

Based on genome-wide profiling, many corticosterone-responsive hippocampal mRNAs—also in laser-dissected subregions—are known, allowing the identification of specific signaling pathways [34–37]. In other brain areas, information is more sparse, but likely will differ substantially, as patterns of MR and/or GR-responsive target genes overlap only partially between different cell types [38]. This cell specificity seems to be the consequence of a different chromatin organization and of cell-specific expression of coregulatory proteins that modulate the effects of MR and GR, once these are bound to the DNA [39, 40].

In view of their very different effects in the hippocampus, MR and GR should have unique target genes, and this assumption indeed recently has been materialized in three independent studies [31, 32, 41]. A unique signature of MR binding to DNA loci was discovered and found associated with the NeuroD transcription factor [33]. Also GR binding appeared associated to some extent with NeuroD, possibly as a result of heterodimer formation with MR [42]. Furthermore, current data suggest that NeuroD can interact with other unidentified proteins in the transcriptional complex that is formed upon MR binding to DNA. Such a MR-Neuro-D complex seems to confine specificity to cortisol action.

In spite of this progress in understanding receptor-specific cortisol actions, there is no single GR or MR target gene known to be responsible solely for circuit activation underlying a particular behavioral response during stress adaptation. Rather, MR and GR seem to be master regulators that mediate in complementary manner downstream regulatory networks in a cell- and context-specific fashion [37, 43]. Moreover, the transcriptional response of the hippocampal genome to corticosterone depends strongly on the recent past of the individual. About half of the significantly regulated mRNA's were found to be different between animals with a recent history of stress, as compared to control animals [37, 44].

4. Cellular mechanisms of MR-/GR-mediated action

In hippocampal CA1 neurons, in particular the membrane properties affected by norepinephrine (NE), serotonin (5HT), and glutamate are affected by corticosterone in a U-shaped dose-response curve [45, 46]. Thus, the activation of 5HT1A receptors produced during absence of corticosterone a large increase in conductance of an inwardly rectifying K-channel, causing the membrane to hyperpolarize. MR activation with a low concentration of corticosterone minimized the 5HT1A hyperpolarization response [47]. When corticosterone levels increased and gradually occupied GR, the hyperpolarization response returned, but not in $GR^{dim/dim}$ mutants [48], in which cannot dimerize because of point mutation in their DNA domain [49]. A similar U-shaped dose response was found for the accommodation of firing frequency upon steady depolarization of cells by NE and for the Ca influx via L-type voltage-dependent channels [46, 50–52].

The U-shaped dose-response curve is not a common phenomenon in the brain, since it is dependent on the presence of both receptor types. Even if both receptors are present, such as in the dentate gyrus, other membrane properties are affected than in the CA1 neurons. In the dentate gyrus MR activation increased the field potential, and the single cell response showed activation of glutamatergic receptors, and both responses were not further affected by additional GR activation

[46]. These cellular effects in CA1 and dentate gyrus have not been explained by transcriptional regulation. For instance, 5HT1A mRNA expression in CA1 cells was not affected by adrenalectomy, while it was in an MR-dependent fashion in dentate gyrus neurons [53].

The dentate gyrus is one of the two brain regions where neurogenesis occurs throughout life. In the absence of steroids, the turnover of these neurons increases, showing increased neurogenesis and apoptotic cell death. Both processes are normalized if the animals are replaced with low doses of corticosterone, just sufficient to occupy MR. Glucocorticoids suppress proliferation and migration of the newborn neurons via GRs. Lentiviral GR knockdown in the dentate progenitor cells accelerates neuronal differentiation and migration. The newborn neurons showed increased synaptic contacts and increased excitability and migrated further in establishing functional integration in the hippocampal circuitry. Accordingly, contextual fear-motivated behavior was impaired [54].

Regarding the non-genomic actions, MR mediates the rapid and transient increase of miniature excitatory postsynaptic currents (mEPSC) after treatment with corticosterone. The putative membrane MR is localized presynaptically and activates the release probability of glutamate. The rapid effects were eliminated after genetic deletion of the MR gene or with MR antagonists [55]. These effects are exerted by both aldosterone and corticosterone, and the dose-response curve suggests a lower affinity of steroid binding to the membrane than to nuclear MR. The membrane MR—in spite of much effort—has not been physically demonstrated yet [56–58] and likely is similar to the nuclear variant. The MR-enhanced increase of glutamate release downregulates the presynaptic metabotropic glutamate receptors ($mGluR_2$) [59].

The nature of the membrane-mediated MR effects shows, however, large regional differences in the brain. For instance, in contrast to the rapid transient rise in excitability, the excitation is long-lasting in basolateral amygdala (BLA) neurons due to cooperation with genomic GR-mediated actions. Moreover, the duration of BLA excitation is further prolonged if—as is the case during stress—these cells are also exposed to NE, which can be mimicked by the β-adrenergic agonist isoproterenol. Interestingly, such a prolonged increased excitability of the BLA protects against the effect of a second MR-mediated corticosterone pulse, probably via rapid endocannabinoid action linked to the membrane GR [60]. These composite cellular responses were defined as a manifestation of "corticosterone metaplasticity" and may explain why emotions are so strongly remembered [61, 62].

Thus, the data demonstrate that glucocorticoid actions may vary between cell groups. This variety in responses also has consequences for the influence of stress exposure and stress hormones on long-term potentiation (LTP), a cellular model of memory performance. It demonstrates that stress does not a priori disturb LTP, since the outcome depends on the context, the previous experiences, the phase of the stress response, and the analyzed brain regions [63]. In the hippocampus, MR is essential for neuronal viability and maintenance of excitatory transmission. If, with increasing corticosterone concentrations, GR becomes occupied, this receptor restores transiently raised excitability.

5. Functional cooperation of MR and GR

MRs and GRs cooperate in glucocorticoid regulation, and below we will distinguish four different phases of this cooperation in stress coping and adaptation (see **Figure 1**). This distinction is based on temporal and contextual features of membrane and genomic glucocorticoid actions. The conditional nature is an important

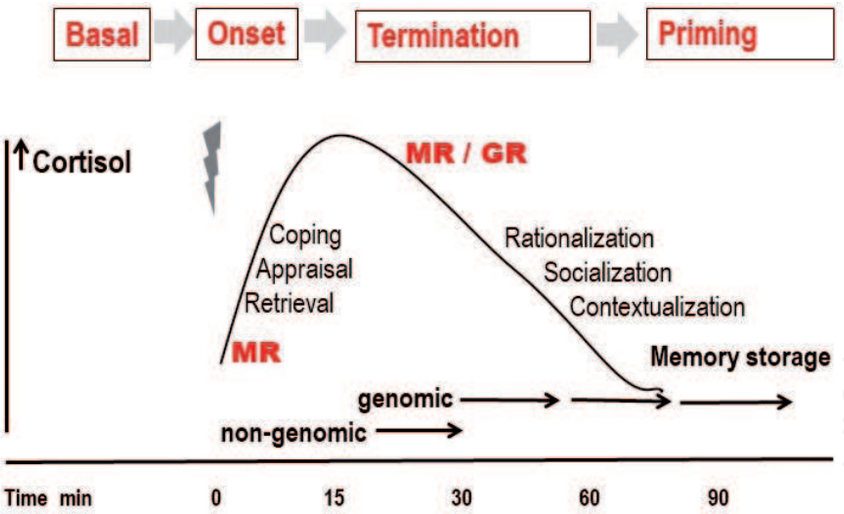


Figure 1.
Four phases of MR/GR signaling in the brain during the stress response. ***Phase 1****: "Basal" MR/GR signaling during ultradian/circadian activity is a determinant of the sensitivity of the stress response.* ***Phase 2****: "Onset" of the stress reaction non-genomic MR-mediated actions promotes appraisal processes, retrieval of previously stored information, selection of coping style, and encoding of the experience for learning, all directed to defend the "self."* ***Phase 3****: "Termination" is the negative feedback action of GR-mediated glucocorticoid action aimed to prevent defense reactions from overshooting. Via GR, the experience is contextualized in the hippocampus and rationalized in the prefrontal cortex, with more "altruistic" solutions that increase motivation to assign a valence to social solutions and rewards.* ***Phase 4****: "Priming" refers to memory storage of the experience for future use (adapted from [27, 28, 64, 65]).*

criterion, since it assigns a specificity to glucocorticoid action. The temporal action is also critical. The rapid non-genomic actions wax and wane in correspondence with glucocorticoid concentrations. The genomic actions develop minutes to hours after glucocorticoid exposure and may last for days or even a lifetime. The latter concerns aspects of programming of brain circuitry for later life by epigenetic processes at glucocorticoid targets or even the receptors themselves [66]. The following phases in glucocorticoid action can be distinguished:

Phase 1—basal is the basal state in which during the circadian/ultradian cycle, mostly genomic MRs are occupied during the trough, and, subsequently, when glucocorticoid levels show their hourly increases, the hormone progressively activates additional GRs. The continuous MR activation is a determinant of the threshold or sensitivity of the stress response system. The transient GR activation by the hourly pulses maintains responsivity to sudden changes in glucocorticoid secretion as they occur in response to stress [3, 9, 67].

Phase 2—onset is the onset of the stress reaction when a novel experience is anticipated or actually happens and triggers sympathetic activation and CRH release. Non-genomic MRs that are rapidly activated by a stress-induced increase in circulating glucocorticoids enhance attention and vigilance to optimize sensory processing in support of perception and appraisal of novel information [68]. MR activation promotes memory retrieval in the hippocampus to deploy the previously used strategy in stress coping and enhances in amygdala emotional expressions of fear and aggression [69, 70]. MR activation also facilitates the choice of coping style. For instance, under mild stress conditions, most individuals will opt for a coping strategy involving the hippocampus (thinking). However, when stressors become more severe and less controllable, increasingly an emotion-driven habitual amygdala-striatal stimulus-response coping strategy is preferred (doing). The switch from "thinking to doing" depends on limbic MR. Corticosterone administration promotes habit formation, while MR antagonists prevent the switch and the slower, costlier hippocampal cognitive strategy

is maintained. Finally, via MRs the context of the experience and the selected coping style are encoded for learning [71–73].

Phase 3—termination marks a further increase of glucocorticoid secretion and progressive activation of the lower-affinity membrane and genomic GRs, which are in limbic-frontocortical structures co-localized with MRs [25, 28]. The MRs are continuously involved in appraisal processes to monitor the outcome of the stress-coping strategy. GR function limits defense reactions to prevent these from overshoot that may cause damage, if not dampened [74]. These defense mechanisms are now abolished, and it is time for *rationalization* and *contextualization* of the experience and for assessment of valence as occurs in *social interactions* [27, 75]. At the same time, GR activation drives via a mitochondrial mechanism energy allocation to cells and circuits in need to facilitate recovery from the stressor [76]. This is a life-sustaining action since complete GR knockouts do not survive, while $GR^{dim/dim}$ do. After all, lack of glucocorticoids is not compatible with life as is illustrated by adrenalectomy and in the case of Addison's disease. Phase 3 is also characterized by increased motivational arousal, emotional expressions, and reinforcement learning, accompanied by increased gene expression of key components in the amygdala (re: enhanced CRH expression) and ventral striatum—frontocortical circuitry (re: increased dopaminergic function) [77–81].

Phase 4—priming GR activation in the limbic-frontocortical circuits promotes storage of contextual and emotional-loaded information in the memory. This consolidation process takes a couple of hours after the stressful experience [82]. Synaptic adaptations occur which can be measured with fMRI and are characterized by genome-wide transcriptional signatures [83–85]. Growth factors such as BDNF participate by acting in the dentate neurogenic niche; also growth factor actions in e.g. mPFC and mesolimbic dopaminergic systems [86, 87] are all involved. Hence, GR-activated memory storage prepares for the future, so that stored information can be retrieved again in the proper context. During phases 3 and 4, the individual's homeostasis is restored and behavioral adaptation is promoted [4].

Using optogenetics combined with neuroanatomical tracing, the top-down organization of the brain's coping circuitry is rapidly unraveled today. Accordingly, the prelimbic mPFC sends excitatory projections to the lateroventral (av)-BNST, which operates as an inhibitory GABAergic hub over downstream neuroendocrine, autonomic, and behavioral responses [88]. Stressors activate the excitatory output of the mPFC, which translates into BNST-dependent inhibition of CRH neurons in the PVN and results in suppression of the HPA axis response. In another group of CRH neurons, the BNST input attenuates the sympathetic output. A separate pathway of the BNST projects to the ventrolateral periaqueductal (vl-PAG) where passive coping is promoted at the expense of the initial active coping strategy [89, 90]. Active coping refers to fight or flight, which, when the situation is appraised as inescapable, causes a reorganization of prelimbic to infralimbic mPFC circuitry that is aimed to restrain the emotional and autonomic responses [91–94]. Passive conservation withdrawal behavior is promoted allowing recuperation and storage of energy resources [95, 96].

This coping circuit is modulated in function by contextual information from the hippocampus, by emotional- and fear-input from the amygdala, visceral and autonomous inputs from the brain stem, and motivational arousal associated with valence assessment from the ventral striatum. The coping circuit and its modulating inputs are all targets of the glucocorticoids that convey environmental and physiological information. This bottom-up control exerted by the glucocorticoids is mediated by the MR and GR in a complementary manner along the four different phases of stress coping and adaptation [64] (see **Figure 1**). The action of the glucocorticoid during stress coping and adaptation has led to the formulation of

the MR/GR balance hypothesis, which states that "upon imbalance of the 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" [9, 25, 28, 97–99].

6. Implications for pathogenesis and treatment of stress-related diseases

Physical or psychogenic stressors promote activation of circuits that underlie appraisal and decision-making processes, which are important for selection of an appropriate coping style to support physiological and behavioral adaptations. The most severe psychogenic stressor is lack of control and inability to predict, with an uncertain fearful feeling [96, 100]. The brain can adapt to this situation by proliferation of the emotional amygdala and atrophy of the hippocampus, ventral striatum, and prefrontal cortex [101–104]. Glucocorticoid secretion remains elevated and energy resources are drained. Essential defense mechanisms become compromised, and when then confronted with a novel stressor, coping fails, breakdown of adaptation is facilitated, and vulnerability to mood and anxiety disorders increases [105, 106].

Adverse (early) life experience and unfavorable socioeconomic conditions are important predisposing factors for such stress-related disorders [107]. Also genetic variants and epigenetic modifications are increasingly recognized as biomarkers of susceptibility and vulnerability. For instance, for MR, two functional SNPs (rs2070951 and rs5522) constitute a block of four haplotypes. Haplotype 2 generates in vitro the highest MR-binding capacity and transactivation. Carriers of haplotype 2 display a preferential *habit* rather than *cognitive* strategy in coping with stress. Haplotype 2 (C/A frequency 35%) is associated with optimism and protection to depression and predicts a higher efficacy of antidepressants [73, 108–110]. Actually, the MR is a promising target to facilitate the action of antidepressants [111].

Progress is made in exploiting the relevance of the MR/GR balance for devising preventive or curative strategies in the treatment of mental health. For instance, it is recognized that patients under dexamethasone therapy have very low levels of endogenous circulating glucocorticoids. While dexamethasone is a potent GR ligand, the MR becomes depleted of endogenous hormone, because of suppression of the HPA axis. Refill of the MR with cortisol add-on largely eliminates the psychologic/psychiatric side effects of dexamethasone therapy [112–115]. Alternatively, the glucocorticoid/progesterone antagonist mifepristone is applied for treatment of hyperglycemia in patients suffering from Cushing's syndrome [116]. Recently, selective GR modulators (SGRMs) became available that can target metabolism but do not show side effects on pituitary ACTH release [117–119].

7. Concluding remarks

Glucocorticoids, acting via brain MRs and GRs, coordinate multiple functions over time with one single goal: to promote stress coping and adaptation. Imbalance in the MR-/GR-mediated signaling pathways increases susceptibility to stress-related mental and neurodegenerative disorders. These imbalances develop under conditions of chronic stress when top-down control exerted by the mPFC over the stress-coping circuitry is compromised and the cost of bottom-up glucocorticoid action exceeds its benefit. New SGRMs are being developed that target the tissue- and context-specific action of glucocorticoids in specific domains of cognition, emotion, and motivation and which may assist in targeted therapies of stress-related mental disorders.

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Conflict of interest

ERdK is on the Scientific Advisory Board of the DynaCorts Group and owns stock of Corcept Therapeutics. OCM receives funding from Corcept Therapeutics.

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