Glucocorticoid and Mineralocorticoid Receptors in the Brain: A Transcriptional Perspective

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Adrenal glucocorticoid hormones are crucial for maintenance of homeostasis and adaptation to stress. They act via the mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs)—members of the family of nuclear receptors. MRs and GRs can mediate distinct, sometimes opposite, effects of glucocorticoids. Both receptor types can mediate nongenomic steroid effects, but they are best understood as ligand-activated transcription factors. MR and GR protein structure is similar; the receptors can form heterodimers on the DNA at glucocorticoid response elements (GREs), and they share a number of target genes. The transcriptional basis for opposite effects on cellular physiology remains largely unknown, in particular with respect to MR-selective gene transcription. In this review, we discuss proven and potential mechanisms of transcriptional specificity for MRs and GRs. These include unique GR binding to "negative GREs," direct binding to other transcription factors, and binding to specific DNA sequences in conjunction with other transcription factors, as is the case for MRs and NeuroD proteins in the brain. MR- and GR-specific effects may also depend on specific interactions with transcriptional coregulators, downstream mediators of transcriptional receptor activity. Current data suggest that the relative importance of these mechanisms depends on the tissue and physiological context. Insight into these processes may not only allow a better understanding of homeostatic regulation but also the development of drugs that target specific aspects of disease.

Adrenal glucocorticoid hormones support physiology and are essential for the adaptive response to stress [1, 2]. The main glucocorticoid in humans is cortisol, whereas in rodents it is corticosterone [3]. An important target organ is the brain, where the action of these corticosteroids is mediated by the high-affinity mineralocorticoid receptor (MR) and the lower affinity glucocorticoid receptor (GR). Given its high affinity, MR is occupied at basal hormone levels, whereas GR is activated at the circadian peak of glucocorticoid secretion and during stress [4]. The dominant ligands of brain MRs are cortisol and corticosterone. Selective brain regions contain MR, which binds aldosterone to control physiology and behavior in relation to salt balance. This occurs in the nucleus of the solitary tract where MR-expressing neurons enzymatically convert glucocorticoids into the inactive form

Abbreviations: DBD, DNA-binding domain; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HPA, hypothalamic-pituitary-adrenal; MR, mineralocorticoid receptor; nGRE, negative glucocorticoid response element.

cortisone via 11β-hydroxysteroid dehydrogenase type 2, allowing access of aldosterone to the MR [5, 6].

GR is present in most brain regions and cell types, whereas MR is mainly expressed in limbic areas such as the hippocampus, amygdala, and prefrontal cortex [7]. GR and MR control a wide range of processes, ranging from neuronal differentiation [8] and excitability [9] to behavioral reactivity, mood, and cognition [2]—all processes that are needed to adapt to acute or chronic stress. MR activation during the early phases of acute stress is important in the appraisal process and memory retrieval; GR complements this by promoting memory consolidation and behavioral adaptation [2]. In addition to complementary actions of GR and MR, they can also exert opposing effects, even within the same cell type. This is best demonstrated by the excitability of hippocampal CA1 neurons, which are stimulated via MR and suppressed by GR activation [9]. However, differential effects of MR and GR are not limited to the brain; they also take place in the immune system, where MR-mediated proinflammatory effects contrast with the classical GR-mediated immune suppression [10], and in the heart [11].

The distinct effects of GR and MR in the brain are reflected in glucocorticoid effects on psychopathology. For instance, overactivation of GR is considered a risk factor for development of mood disorders. Patients with Cushing syndrome are exposed to excessively high cortisol levels and experience psychiatric symptoms such as personality changes, anxiety, irritability, and depressed mood. The use of a GR antagonist can relieve these symptoms [12–14]. On the other hand, low MR activity has been linked to psychiatric disorders. Observationally, in depression, schizophrenia, and bipolar disorder, there is decreased MR expression [15]. Genetically, MR gene variant haplotype 2 is known to enhance MR activity and is associated with lower risk of depression in women, indicating perhaps an interaction with sex steroids [16]. Clinically, a trial with an MR agonist as add-on treatment to antidepressant medication led to a faster antidepressant response in patients with major depressive disorder [17]. The protective effect of high levels of brain MR signaling may reflect direct effects on excitability in the limbic brain. It has also been proposed that lowered MR activation may lead to loss of its tonic inhibition of the hypothalamic-pituitary-adrenal (HPA) axis, causing chronically elevated cortisol levels. Subsequently, this high cortisol level increases the risk for major depressive disorder after a stressor [15, 18].

A recent argument for a direct effect of MR activation on mood comes from the use of synthetic glucocorticoid medication, which is known to cause adverse psychological, behavioral and cognitive effects [19, 20]. An example is the synthetic glucocorticoid dexamethasone, which is highly selective for the GR *in vivo* [21]. Dexamethasone strongly activates GR, which leads to suppressed HPA axis activity and reduced cortisol levels, thereby depleting MR of its ligand. The psychological adverse effects of dexamethasone may either be caused by GR overactivation, MR underactivation, or a disturbed balance in GR and MR activity [22]. A recent clinical trial demonstrated that psychological adverse effects and sleep-related difficulties caused by dexamethasone can be alleviated by reactivating MR with cortisol cotreatment [23]. This indicates that MR activation has an important role in stress-related psychopathology (*i.e.*, in the context of high levels of GR activation).

Although it is established that MR and GR have differential intrinsic effects in the brain, it is unclear how these are established. In fact, MR and GR share not only basic mechanism of action but also target genes. We discuss proven and potential transcriptional mechanisms that can underlie transcriptional specificity for GR and MR.

1. Mechanisms of Action

MR and GR evolved from a common ancestral corticosteroid receptor gene; they share their basic overall nuclear receptor structure, with a central DNA-binding domain (DBD) and a c-terminal ligand-binding domain. These domains are similar enough to have overlap in, for example, ligand binding to the receptors and DNA binding by the receptors. Yet, some crucial mutations led to unique differences not only in ligand binding specificities but also in functionality [24–26].

A. Nongenomic Effects

Corticosteroids have well-documented, rapid effects that occur independently of DNA binding. Although they may be mediated via other mechanisms than binding to MR and GR [27], many of these effects in the brain are absent in MR/GR knockout mice [28, 29]. Nongenomic effects also occur via aldosterone-activated MR in the vasculature [30]. The MRs and GRs that mediate these rapid effects may be localized at or near the membrane (via unknown mechanisms). Nongenomic effects may also follow the dissociation of the receptors from their chaperones in the cytoplasm [31]. Of note, the pharmacology of the membrane-associated effects differs from the classical genomic effects in that higher hormone concentrations are needed to exert effects via membrane-associated receptors [28, 29]. For glucocorticoids secreted in response to stress, the nongenomic effects may support initial responses by rapid mediators such as noradrenalin, particularly with regard to MR-dependent effects [32, 33]. Interestingly, the nongenomic signaling does not simply precede genomic effects of the same episode of hormone secretion; it may also set the context for the genomic effects in a process called metaplasticity [34].

B. Glucocorticoid Response Elements

Genomic steroid receptor effects depend on at least three different processes: ligand binding, receptor association to the DNA, and interactions with other transcriptionally active proteins [35, 36]. As members of the nuclear receptor family, MR and GR translocate to the cell nucleus upon binding of hormone and can bind to glucocorticoid response elements (GREs) via the DBD. This occurs mainly in accessible chromatin, but at least GR can also pioneer the remodeling and opening of chromatin [37]. Dependence on accessible chromatin is one of the reasons that most putative GR-binding sequences are, in fact, not occupied by receptors and do not constitute actual GREs. Interactions of the receptors' transcriptionally active proteins also determine whether a GRE sequence actually is a functional GRE [38]. The consequence of these interactions is that evolutionary conservation of GRE sequences is a predictor of functionality [39].

The DBD is 96% identical between MRs and GRs, and, therefore, they share the same GRE as their primary binding motif. GREs consist of inverted repeats to which the receptors bind as homo- or heterodimers [40, 41]. Recently there have been suggestions of higher-order complexes at the GR, with these complexes consisting of tetramers, and/or MRs that interact with DNA-bound GR, independent of the MR DBD [42, 43]. It seems that for GR, the homodimer binding to the GRE alone is not the final active form but rather it triggers tetramerization of GR, thereby adding an extra level of regulation [43]. MR interactions with the GRE-bound GRs may be a variation on this theme [42]. In addition, there can be cooperation between receptors that are bound to GREs and GRE half sites that are in close (functional) proximity [44, 45]. Binding to these GREs is normally linked to target gene activation rather than repression [24].

Once the agonist-bound receptors are bound to GREs on the DNA, they recruit coactivator and corepressor proteins that form the bridge to the transcription-initiation complexes [46]. The coregulator recruitment depends critically on the exact receptor conformation, which is determined by amino acid sequence, the ligand that is bound [47], and the DNA element to which the receptor is bound [48, 49]. The fact that coregulator interactions depend on the exact DNA-binding sequence predicts that specific coregulators are critical for specific sets of MR and GR target genes. Indeed, this is clearly the case, for example in relation to GR signaling in the brain: steroid receptor coactivator 1 (SRC-1) is a coregulator of GR and is necessary for the regulation of the *Crh* and *Pomc* genes, but not *Fkbp5* [50, 51].

MR and GR recruit coregulators via two domains or activation functions: AF-1 is located in the intrinsically unstructured *N*-terminal part of the receptors [52], whereas AF-2 is formed in the highly structured ligand-binding domain [45]. Receptor-coregulator interactions via AF-2 can be studied using an *in vitro* peptide array called MARCoNI [53]. This array recapitulates ligand-induced interactions based on coregulator-derived peptide sequences:

Agonists induce interactions with coactivator peptides, while antagonists displace the agonist, reduce coactivator interactions, and, in fact, may lead to recruitment of corepressors leading to active gene repression [46]. Many of these AF-2 interacting coregulators are shared between nuclear receptors, and this is certainly true for MR and GR [54].

C. Negative GREs

The GR is the only steroid receptor that can also bind to negative GREs (nGREs), at which two receptor molecules bind, but which does not require dimerization of these receptors [24, 55]. At the nGRE, the receptor adopts a different conformation, is SUMOylated in its *N*-terminal domain, and recruits corepressors such as NCOR and SMRT, rather than coactivators [24, 56]. Given that GR agonists do not induce such corepressor interactions in DNA-free protein-protein interaction assays [53, 57], it is more difficult to predict the behavior of different ligands at such nGREs. The MR lacks the ability to act via these nGREs, because this requires specific mutations from the ancestral steroid receptor that are unique to GR [24].

D. Protein-Protein Interactions

GR is well known to interact with transcription factors like AP-1 to repress transcription independent of direct binding to the DNA [58]. MR activation, in many instances, also leads to repression of transcription, as evidenced by transcriptomics studies, all outside the brain [11, 59]. Because nGREs are specific to monomeric GR binding, it seems likely that transrepression of genes via MR depends on interactions with other transcription factors. Interactions between MR and transcription factor SP-1 may be a case in point [37, 60]. The use of such tethering mechanisms is highly tissue specific. In a genome-wide characterization of DNA-binding sites for aldosterone-activated MR in a human kidney cell line, the majority of loci contained no apparent GRE but rather binding site motifs for transcription factors like EGR1, FOX, PAX5, and AP-1 [61]. In contrast, motif analysis of genomic MR binding in the rat hippocampus suggested exclusive binding to GRE-like sequences [62]. Also GR binding in the rat hippocampus, but not in cell lines, seems to be predominantly GRE dependent [63–65].

Thus, the cistromes of MR and GR in the hippocampus point to a predominance of GRE binding. However, corticosterone clearly suppresses the expression of many hippocampal genes [66, 67]. The part of the MR cistrome that might be associated with transrepression, as previously identified for individual genes [60, 68], therefore, is unclear. A caveat regarding the current experiments on the brain (and other tissue homogenates) is that binding events in specifically activated neurons (*e.g.*, after learning tasks) may have been diluted beyond detection. On the other hand, results in cell lines may be relevant for mitotic cell populations, and obviously, by definition, are not in a physiological context. A full overview of all the cross-talk partners in different cells and tissues awaits dedicated experiments in different physiological settings.

Of note, although classical protein-protein transrepression depends on tethering of MR and GR, there are also hybrid mechanisms by which GR directly binds to DNA near transcription factors like AP-1 as a compound GRE [69, 70]. As with tethering mechanisms, the outcome of GR activation may be repressive or rather synergistic, depending on the exact nature and spacing of the interacting partners. Composite elements are important for recruitment of GR to the chromatin via transcription factor AP-1 [71]. Variations on this theme are the codependence of MR or GR binding to GREs in conjunction with other transcription factors that may require longer-range interactions on the DNA [38, 72].

2. Mechanisms for MR Specificity Over GR

Foremost, the presence or absence of the receptors in a cell will determine whether cortisol will act via MR and/or GR. Differential effects of MR and GR activation in physiology may be explained in part by targeting of different cell types in the body that may or may not express either receptor. Single-cell sequencing will reveal, in the near future, the MR-to-GR ratio at

the mRNA level for any cell type in the brain, as has been done already for the human temporal cortex, where 69 types of neurons were identified [73]. Figure 1 shows relative GR and MR expression in these cell types. For now, the current literature suggests there may be dominant MR presence in CA3 pyramidal cells in the hippocampus, even if GR is also present [74], and some GABA-ergic cortical neurons. MR-exclusive cells have not been proven, although one may expect that in neurons with aldosterone-selective MR, there should be very little GR activity.

When MR and GR are coexpressed, they can differentially affect cellular physiology. This is exemplified by the classical U-shaped effect of corticosterone on excitability of hippocampal CA1 neuron. In these cells, MR activation stimulates excitability by suppressing the responsiveness to 5-HT1A receptor and calcium currents. Concomitant GR activation has the opposite effects on these cellular responses. In this way MR and GR mediate opposite effects of different doses of corticosterone on neuronal excitability [9].

At the mRNA level, the single-cell sequencing studies will help fine tune our understanding of where MR and GR can exert their effects in complex tissues like the brain [73]. At the protein level, knowing the relative abundance of MR and GR is complicated by technical issues (*e.g.*, dependence on antibodies) and by the existence of MRs and GRs that differ in the length of their *N*-terminus because of alternative translation of their mRNAs [75, 76]. Also posttranslational modifications will affect the relative activity of the receptors [77].

There are several options as to how MR and GR differentially affect transcription, if they are both present in the same cell, including binding to specific GREs (potentially in conjunction with other transcription factors), differential binding to nGREs, differential
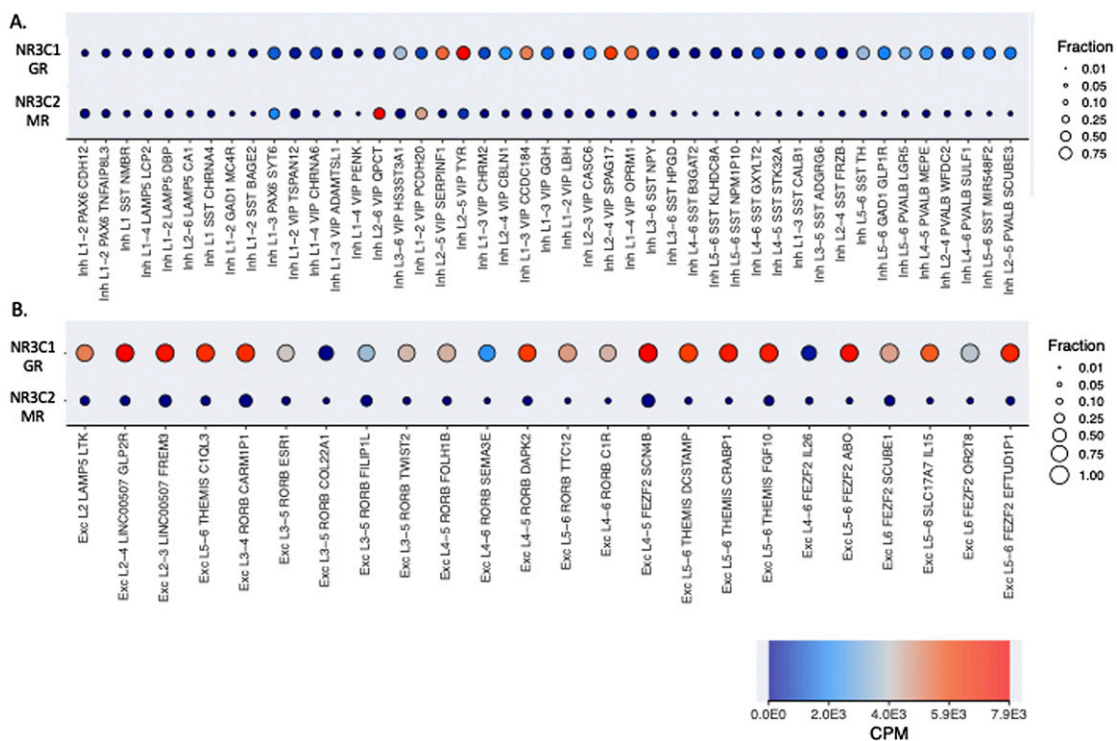

Figure 1. Expression of GR and MR in all individual 45 inhibitory and 24 excitatory neuronal cell types of the human temporal cortex. (A) GABA-ergic ('inh', or inhibitory) neurons show variable expression of GR and MR. Two GABA-ergic neurons show higher expression of MR than of GR: layer 2-6 VIP/OPCT positive neurons and layer 1-2 VIP/PCDH20 positive neurons. In most cell types, receptors are expressed at intermediate to low levels. (B) Glutamatergic ('Exc', or excitatory) neurons generally express high levels of GR and low levels of MR. Exonic expression is shown. Color codes for counts per million (CPM) transcripts on a linear scale, and size indicates the fraction per cell types with expression >1 CPM. Data and image are from http://celltypes.brain-map.org/rnaseq/human.

interaction with other transcription factors, and differential interaction with downstream coregulators once the receptors have bound to the DNA. It is clear that binding to negative GREs is exclusive for GR [24]. It was also noted early on that GR is more potent than MR at transrepression of the transcription factor AP-1 [78]. Such effects may explain unique effects of cortisol via GR, such as anti-inflammatory effects, but MR also has intrinsic effects that differ from those mediated by GR [9, 10].

A. DNA Binding

In the rat hippocampus, we were able to make a direct comparison between whole-genome MR and GR binding in the same samples 45 minutes after treatment with a high dose of corticosterone. This revealed many DNA loci that were bound by either MR, GR, or both receptors. Motif analysis suggested that the GRE sequence was present in all bound DNA fragments, although the consensus sequence was slightly more degenerate for MR binding sites [62, 63].

Strikingly, the consensus binding site for NeuroD factors always co-occurred with the GRE for MR-specific binding sites but not for GR-specific binding sites. This motif was also reported for ~15% of all GR binding sites in a separate study [64], and we suggest these loci represent sites where both MR and GR can bind either as homo- or as heterodimers [40]. Chromatin immunoprecipitation experiments confirmed the presence of the NeuroD2 protein, typically within 300 nucleotides of the MR binding site on hippocampal DNA. In forebrain-specific MR knockout mice, NeuroD2 was still present at these sites, suggesting that any functional directionality involves binding of NeuroD2 before MR [79]. Therefore, NeuroD factors may selectively allow MR binding to GREs in the principal neurons of the hippocampus. Complete absence of MR, in most cases, did not lead to GR binding at the shared MR and GR loci, nor did GR bind to specific MR loci in the MR-knockout mice. Competition between MR and GR for DNA binding, therefore, does not seem to be a dominant mechanism. However, in absence of MR, GR binding was increased at the *Per1* locus [79]. This may be related to the fact that this particular GRE is a very high affinity GR binding site, given the very low EC_{50} value for glucocorticoid induction of the *per1* gene [80].

How NeuroD would confer MR-specific DNA binding is not fully understood. The somewhat more degenerate GRE consensus for MR-selective loci may point to the necessity of NeuroD proteins as stabilizing factors for MR binding at these loci, but this remains to be proven. Structure-function analysis of MR and GR interactions with NeuroD in cell lines did not recapitulate the MR specificity: In transient transfections, NeuroD binding near a GRE could potentiate both MR- and GR-mediated transactivation. This may be explained by an incomplete chromatin context of transfected plasmids and/or reflects interactions of NeuroD factors with a third factor that is present in hippocampus but not in cultured cells. The notion of indirect interactions between MR and NeuroD factors is supported by additional studies in cell lines in which NeuroD proteins potentiated corticosterone-induced transcription of both *N*- and C-terminal truncations of MR and GR [62].

NeuroD proteins form a subfamily of bHLH transcription factors and have an important role in the terminal differentiation of particular neurons [81, 82]. Family members NeuroD1, 2, and 6 are expressed at substantial levels in different subfields of the adult mouse and rat hippocampus [62]. The link with neuronal end differentiation may explain the much more limited neuronal expression of MR compared with GR, in that MR would be specific only to particular differentiation programs. The intrinsic connection of MR binding sites to NeuroD factors suggest that via MR basal glucocorticoid levels are linked to the "neuron-ness" of such cells. This may relate to the early electrophysiological findings that showed increased excitability of the principal neurons in the hippocampus upon MR activation [9]. Of interest, NeuroD proteins have been found differentially expressed in postmortem brain tissue of depressed subjects [83].

NeuroD proteins are closely related to the MyoD family of transcription factors, which plays a role in the differentiation of muscle. MyoD factors can bind to a subset of NeuroD

response elements and are somewhat better understood in terms of structure-function relationship [84]. MyoD family members may regulate gene expression either by direct transcriptional activation or by remodeling of the local chromatin [85]. In reporter studies, MR responses were affected only by the chromatin-modification function rather than the direct transcriptional activation. In contrast, GR-dependent transcription was potentiated by MyoD proteins via both mechanisms [79]. Knockout models for individual NeuroD factors may suffer from early death [86] and absence of particular neuronal populations [87], but on the other hand, they may show compensatory upregulation of family-member bHLH protein [88]. Nevertheless, in (inducible) models that show survival [86, 89], it will be very interesting to test MR functionality in the hippocampus.

As in the NeuroD study, GR seemed to be a much stronger transcription factor in reporter studies [44], but this seems at odds with powerful *in vivo* observations, both in terms of gene expression [90] and DNA binding [62]. Of note, in other cell types, functional interactions between MyoD and GR have been observed [91]. Thus, there seems to be a more general interaction mechanism between MR and/or GR and bHLH transcription factors that is dependent on yet different factors, given the cell specificity of the effects. For the hippocampal loci where MR and GR bind, NeuroD may help recruit MRs, also in the face of high hormone concentrations that would otherwise bias toward exclusive GR binding. Thus, on one hand, joint MR and GR occupancy may simply extend the dose-response curve for endogenous glucocorticoids and, on the other hand, fine tune the magnitude of transcriptional responses by, for example, heterodimerization.

B. Coregulators

It is clear that some coregulators are shared by MR, GR, and a host of other nuclear receptors, in particular for the AF-2 domain that is highly structured and similar between related nuclear receptors [53]. It is also clear that there is coregulator specificity, not only per receptor (in particular, via AF-1 [92]) but also per ligand. For example, coactivators may prefer aldosterone-bound MR to cortisol-bound MR [93, 94].

The final transcriptional outcome of glucocorticoid exposure depends on the type of ligand, type of receptor, the gene, and the cell type. This complexity is an uncomfortable fact if we want to understand and predict steroid action in particular conditions. One way to grasp what may happen in particular cell types is to use coexpression data of receptors and potential coregulators. This was done for all steroid receptors in the mouse brain, based on *in situ* hybridization data from the Allen Brain Institute [95]. The host of current and coming single-cell transcriptomes [73, 96] will allow us to link expression of receptors, their signaling partners, and their potential target genes, and, via "guilt-by-association," pinpoint relevant interaction and predict steroid responses [97].

Ligand-selective coregulator recruitment is one of the mechanisms by which selective receptor modulators act, that is, ligands that combine agonism and antagonism of steroid receptors, dependent on the gene and tissue of interest [98]. Selective modulators induce alternative conformations of the receptors, allowing interactions with only a subset of coregulators [56, 99, 100]. Selective GR modulators have been pursued for a long time, primarily to separate anti-inflammatory effects from adverse effects of glucocorticoid therapy [101]. Selective MR modulators are of interest to block the hypokalemia that comes with MR antagonism aimed at the heart [102]. Conceptually, if stimulating brain MRs would be a therapeutic target [16, 17], selective MR modulation could prevent overactivation of the aldosterone-sensitive MRs regulating blood pressure and salt intake [5].

C. Specific and Shared Target Genes

The existence of unique and shared DNA-binding sites of MR and GR suggests that there will be unique and shared target genes. Transrepressed genes via GR in the activated immune

system are a clear example, but this mechanism appears not to have a major role in the hippocampus [62–64]. The opposite effects of MR and GR on hippocampal excitability have biased the search for target genes toward genes that are uniquely regulated by one receptor type or even in opposite ways via MR and GR.

We used the hippocampal MR chromatin binding profile in the rat to identify MR-regulated genes. Because only ~10% of DNA-bound steroid receptor can be directly linked to gene expression [103], we selected binding sites that were unique for MR located in intronic regions or within 5 kilobases of transcription start sites. Because MR also bound these loci in mouse hippocampal chromatin, we evaluated their expression in mice lacking MR expression in the forebrain [104]. mRNA of *Jdp2, Nos1ap*, and *Supv3l1* was up to 50% less in the brains of the MR-knockout mice, suggesting that these genes are selective MR target genes [105]. Although this list is surely incomplete, and RNA sequencing should reveal other MR-dependent transcripts, the current set of likely MR-specific transcripts may be of use to probe functional MR activity in different paradigms of stress and/or steroid exposure.

It is important that we can attribute particular effects to either MR or GR and evaluate their relative activity in clinical states or experimental models. Having specific readouts for GR and MR activity is not trivial, because the GRE, as such, is shared by both receptors, and most glucocorticoid-induced mRNAs that are routinely used as readouts for glucocorticoid effects can be stimulated via both MR and GR. This includes mRNAs for Per1 [80, 106, 107], Sgk1 [90, 108], and GILZ [109, 110]. In fact, next to some genes associated with selective MR binding, basal levels of FKBP5 mRNA also were substantially downregulated in the hippocampus of forebrain-MR knockout mice [105]. That target genes are shared suggests (in well-studied cases) MR and GR cooperate to extend the cellular sensitivity for glucocorticoids over a range of three orders of magnitude. Functionally, the cooperative actions of MR and GR are perhaps made most clear by the fact that both MR and GR mediate negative feedback on the HPA axis. GR mediates negative feedback in pituitary and hypothalamus, and MR does so in the hippocampus [4, 111, 112]. The involvement of both receptor types means that negative feedback takes place in a gradual manner, from minor elevations basal trough levels to very high levels of hormones. The common regulation of genes like FKBP5 also merits attention. Often, FKBP5 function is considered in relation to GR functionality, and the (epi-) genetic variation in the *FKBP5* gene in human disease is likewise being linked mainly or exclusively to GR [113, 114]. Although in some cases (perhaps peripheral blood) this may be justified, the contribution of MR to FKBP5 expression merits a less GR-centric view of this major transcriptional target of glucocorticoids. The cellular diversity in the brain calls for more refined experiments to understand which MR and GR target genes are joined, or rather are receptor specific, in which particular cell types.

3. Summary and Conclusions

The cortisol- and corticosterone-preferring brain MR plays an important role in regulation of stress responsiveness, adaption, and mood. It does so via nongenomic and genomic actions in interplay with GR. MR and GR share a number of target genes and may cooperate at the transcriptional level within the cell, as well as at the functional level. MR and GR can also mediate independent effects on gene expression and, in this way, have opposite effects on cellular physiology. MR-specific gene transcripts have been identified, and these seem to depend on a permissive effect of NeuroD factors for MR binding to GREs that mediate transactivation of target genes. More generically, the gene- and cell type–dependent effects of MR and GR on gene expression depend on interactions with several different types of proteins, including transcription factors and coregulators. The coexpression of these interacting partners can be assessed using single-cell sequencing data from repositories or experimental models. Such interactions may be selectively targeted with new receptor ligands, to better understand adaptation to stress, and for therapeutic purposes in stress-related disease.

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Additional Information

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