Diversity of glucocorticoid receptor signaling: molecular mechanisms and therapeutic implications

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General introduction and outline

GENERAL INTRODUCTION

At the beginning of the last century, the physiologist Walter B. Cannon defined homeostasis as the internal "equilibrium"; a balance that is held by constant physiological adjustments [1]. Homeostasis can be challenged by "stressors", as described in 1936 by Hans Selye who wrote: "*Experiments on rats show that if the organism is severely damaged by acute non-specific nocuous agents [...], a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent [...] and represent rather a response to damage as such.*" His observations were the first steps in the theory of stress biology, where stress is defined as a threat to homeostasis [2]. Almost 15 years later, Selye published "Stress and the general adaptation syndrome" in the British Medical Journal, where he argued that any threat to life causes a stress response, and that adequate adaptability and resistance to stress are required for survival [3].

The physiological response to stress

The physiological stress response involves various neuronal and endocrine mediators, including neurotransmitters, neuropeptides, and steroid hormones. The onset of the stress response is associated with the release of catecholamines (*e.g.*, noradrenaline) and the activation of the sympathetic nervous system [4]. The noradrenergic system primarily relies on the locus coeruleus (LC), located in the brainstem. Neurons from the LC project to most brain regions and are the dominant source of noradrenaline in the brain [5–7]. Noradrenaline acts through G protein-coupled receptors, which can cause rapid changes in neuronal electrical properties by altering the functionality of ion channels [8]. Noradrenergic neurotransmission triggered by the LC facilitates the behavioral, cognitive, and neuroendocrine adaptive mechanisms required in the response to stress, particularly those related to vigilance and arousal [9]. LC neurons also activate the sympathetic nervous system leading to the release of acetylcholine in the adrenal medulla which triggers catecholamine release [10, 11]. The sympathetic-adrenal-medullary system connects the rapid response to stress between the central nervous system and the periphery (**Fig. 1A**). The immediate stress response also relies on central release of corticotropin-releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PVN) [12, 13]. The stress response induced by CRH is mediated by CRHR1 receptors that are expressed in the hippocampus, the amygdala and the LC [14–18]. In mice, the selective deletion of CRHR1 in forebrain glutamatergic neurons was shown to alter neuronal activity in the amygdala and the hippocampus, and alleviate anxiety-like symptoms [19]. The neuroendocrine response to stress via the hypothalamic pituitary adrenal (HPA) axis also depends on CRH release by hypothalamic PVN

neurons into the bloodstream, together with arginine vasopressin (AVP) [20]. In rats, it was previously shown that approximately half of the CRH neurons in the PVN are AVP-positive [21, 22]. CRH and AVP that are released from the hypothalamus bind to G protein-coupled receptors (CRHR1 and AVPR1B) in the anterior pituitary gland [23–26] (**Fig. 1B**).

Upon stimulation by CRH, corticotropic cells of the anterior pituitary release the adrenocorticotropic hormone (ACTH) which results from the expression and cleavage of proopiomelanocortin (POMC) [27]. ACTH activates the melanocortin type 2 receptor (MC2R) in the cortex of the adrenal gland, which induces steroidogenesis and immediate secretion of glucocorticoid (GC) hormones [28–30].

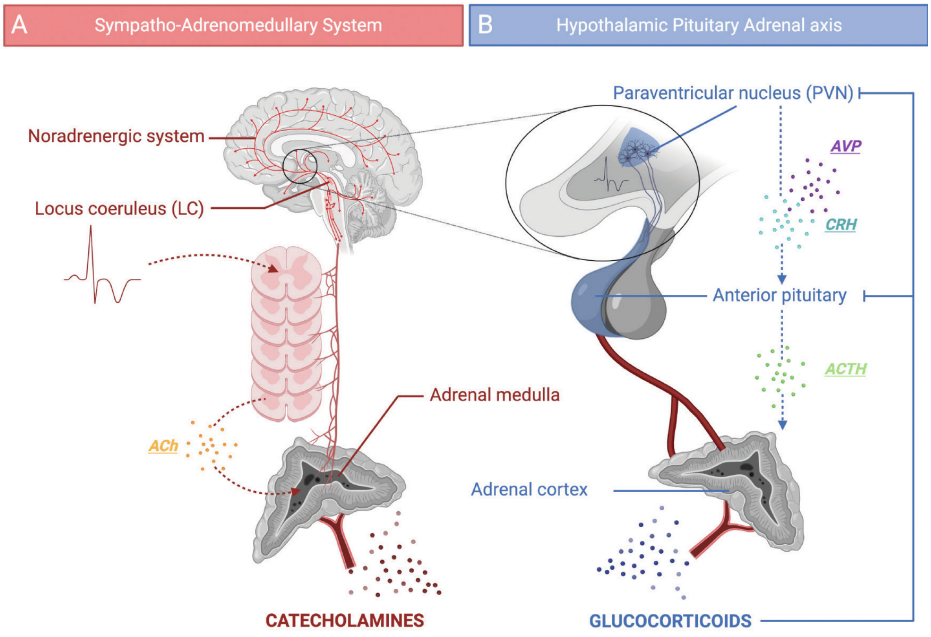

Figure 1. Neuroendocrine response to stress. The sympatho-adrenomedullary system **(A)** and the hypothalamic pituitary adrenal axis **(B)** coordinate the neuroendocrine response to stress. Abbreviations: ACh, acetylcholine; CRH, corticotropin-releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone.

The zona fasciculata of the adrenal cortex produces and secretes the GC hormones, *i.e.*, corticosterone in rats and mice, and predominantly cortisol in humans [31–34] (**Fig. 1B**). To maintain homeostasis, GC hormones exert negative feedback at different levels of the HPA axis, particularly the hypothalamus, and the pituitary (**Fig. 1B**). Some studies have also reported intra-adrenal negative feedback by

GCs, although this phenomenon is less well characterized [35]. Regulation of the HPA axis by GCs also involves cortical and limbic brain regions, including the hippocampus, the amygdala, and the pre-frontal cortex. Indeed, GCs can alter the afferent projections from these regions to the PVN, thereby affecting the activation of CRH neurons [36]. The negative feedback on the HPA axis results in a circadian and ultradian rhythm in GC secretion unto the bloodstream [37].

Upon stress, the increased catecholamine release is rapidly followed by the secretion of GC hormones [38]. Even though both catecholamines and GC hormones have rapid effects to engage energy in response to stress, only GCs can regulate the long-term stress adaptation via genomic and epigenomic mechanisms. These latter effects form the focus of this thesis.

Genomic basis of stress adaptation

GC hormones bind to the glucocorticoid receptor (GR), and the mineralocorticoid receptor (MR) which is also a receptor for aldosterone. Endogenous glucocorticoid levels can be converted into inactive metabolites (*i.e.*, cortisone or 11-dehydrocorticosterone) by the 11β hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme. In tissues that express high levels of 11β-HSD2, MR is predominantly activated by aldosterone [39–41]. In the brain, MR activity is mostly regulated by GCs because 11β-HSD2 is only expressed in a small number of brain nuclei that mediate the central effects of aldosterone on salt homeostasis [42–44]. High affinity of GCs for the MR results in its function as a sensor for basal GC levels, as the dynamic range of MR lies in small variations of hormone concentrations occurring during the circadian trough. On the other hand, GCs have a lower affinity for the GR, and this receptor therefore responds to elevated levels of GCs, during the endogenous circadian peak or upon stress [45, 46]. GR and MR belong to the nuclear steroid receptor family and are encoded by the nuclear receptor subfamily 3 group C member 1 and 2 gene, respectively (*Nr3c1*/*Nr3c2*). Nuclear steroid receptors are ligand-dependent transcription factors composed of an amino-terminal domain (NTD) which contains the activation domain 1 (AF1), a DNA-binding domain (DBD), a hinge region, and a carboxy-terminal ligand-binding domain that contains the activation domain 2 (AF2) [47]. This thesis focuses on the GR which consists of 777 amino acids in mice and diverges from other nuclear receptors mainly in the hinge region and NTD [48].

In the absence of a ligand, a multi-protein chaperone complex sequestrates the GR in the cytosol. FK506-binding protein 5 (FKBP51), and heat shock proteins 70 (HSP70) and 90 (HSP90) are essential to this process [49]. Upon ligand binding,

the cytosolic GR changes its conformation, which exposes its nuclear localization signal [50]. FKBP51 is replaced by FKBP52, which, together with HSP90, induces GR transport into the nucleus using the microtubule network and dynein activity, resulting in a rapid nuclear translocation that is apparent within five minutes [51–55]. This process can also be slower and take up to 50 minutes, which allows GR targeting for proteasomal degradation [56, 57]. In the nucleus, GR associates with DNA at GR-binding sites (GBS). The most common GBS involve a glucocorticoid response element (GRE) with a palindromic sequence (AGAACAnnnTGTTCT). However, the GR can also bind to half sites, or inverted-repeat sites, that are associated with transcriptional inhibition and therefore referred to as negative GREs [47, 58]. Finally, the GR can indirectly interact with DNA by tethering to other transcription factors via protein-protein interactions [59–61].

The GR is thought to be able to bind to DNA as a monomer, although GR homodimers are the favored conformation [62, 63], and GRs could possibly form tetramers (*i.e.*, a dimer of dimers) [64, 65]. The nucleosome consists of histone protein octamers enveloped in DNA. The accessibility of GR to its target loci depends on the nucleosome status of the target region. Chromatin accessibility varies according to post-translational histone modifications and correlates with histone acetylation within genomic active regions. Conversely, histone methylation is often associated with inaccessible heterochromatin (**Fig. 2**).

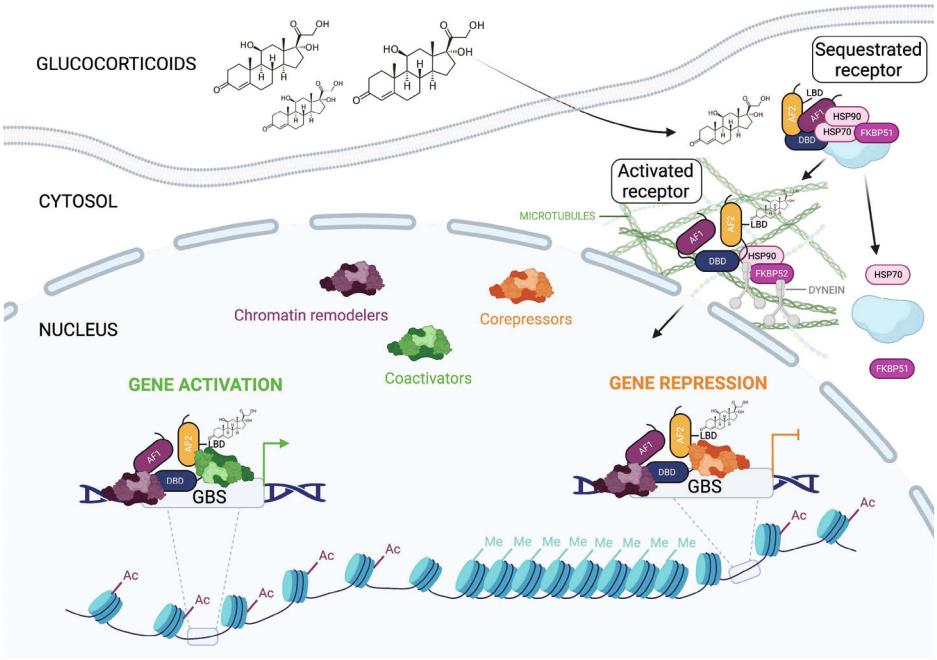

Figure 2. Glucocorticoid receptor transcriptional activity. Abbreviations: AF1, activation function 1; AF2, activation function 2; LBD, ligand-binding domain; DBD, DNA-binding domain; HSP70, heat shock protein 70; HSP90, heat shock protein 90; FKBP51, FK506-binding protein 5 isoform 1; FKBP52, FK506-binding protein 5 isoform 2; GBS, glucocorticoid receptor binding site; Ac, histone acetylation; Me, histone methylation.

At the genome, GR recruits coregulators that determine the outcome of GR signaling. These protein partners can be divided into two main categories: coactivators, that stimulate GR-driven gene transactivation, and corepressors, which lead to gene inhibition by the GR transcription complex. GR coactivators include the p160 steroid receptor coactivator (SRC) family, more specifically SRC-1, SRC-2, and SRC-3, which are also known as nuclear receptor coactivators (NCOA1, NCOA2, and NCOA3). The SRC family is a group of scaffolding proteins that can increase GR stability, but are mostly known to recruit other coregulators, histone acetyltransferases, or histone methyltransferases [47, 66, 67].

Another group of GR coactivators form the mediator complex, which regulates RNA polymerase II activity and the recruitment of transcription initiation factors [47, 68]. GR corepressors mostly include proteins from the nuclear receptor corepressor (NCOR) family and silencing mediators of the retinoic acid and thyroid hormone receptor (SMRT) family [69]. These corepressor complexes contain

histone deacetylases (HDACs) or methyltransferases (**Fig. 2**). A subset of nuclear coregulators can act as corepressors or coactivators depending on the context, *e.g.*, the tissue, cell type or the other proteins present in the transcriptional complex. Finally, the GR interacts with chromatin remodelers to actively change chromatin accessibility around target loci. Particularly, the GR recruits the Brahma (BRM) and Brahma-related-gene (BRG1) SWitch/Sucrose Non-Fermentable (SWI/SNF) complexes [70–72]. BRM and BRG1 are ATPases that catalyze changes in the nucleosome to facilitate chromatin accessibility to the GR transcription complexes (**Fig. 2**) [73–75]. The coactivators, corepressors, and chromatin remodelers compose the GR transcriptional complex and determine the outcome of GR signaling. The GR creates a link between the environment and the genome. The proteins required for the GR genomic activity are differentially expressed between tissues and between cell types, and the composition of the GR transcriptional complex can also be influenced by the context, *e.g.*, in different disease stages, upon stress, and during drug treatment. Consequently, GR signaling is tissue-, cell-, and context specific [76].

Glucocorticoid receptor signaling in metabolic and neuropsychiatric diseases

The GR is widely expressed throughout the body and has pleiotropic functions that both support circadian alignment of tissues as well as adaptation to stress. However, excessive exposure to stressors or GCs, as defined by high intensity, repetition, or prolonged exposure, can lead to maladaptation. Chronic elevations in GC levels can be triggered by chronic stress such as psychological trauma but can also result from repeated and prolonged corticosteroid medication or pathological hypercortisolism, as occurs in patients with Cushing's syndrome. The immune system is one target of GR signaling. The acute stress response in part via GCs enhances adaptive immunity, but GCs are best known for their anti-inflammatory effects to counteract an excessive initial response to infections [77]. As a deleterious consequence, chronic GC exposure disturbs immune responses by decreasing the number and activity of immune cells (leukopenia) [78, 79]. In addition, excessive exposure to GCs can trigger and exacerbate metabolic diseases. Cushing's syndrome is an extreme example of the extent of metabolic consequences of uncontrolled GR signaling. Hypercortisolism in patients with Cushing's syndrome leads to metabolic abnormalities, such as hyperlipidemia, hyperglycemia, and insulin resistance [80, 81]. GC medication for inflammatory diseases is associated with the same cluster of metabolic disturbances [82–85]. As an example, excessive GC exposure or chronic stress in conjunction with high-fat diet can lead to non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH) [86, 87]. The prevalence of NAFLD in patients with Cushing's syndrome is approximately 20% [88].

GC-induced liver lipid accumulation is attributed to increases in food intake, gluconeogenesis, lipogenesis, fatty acid uptake, and inhibition of lipid β-oxidation [86, 89]. Yet another side effect of synthetic GCs is the suppression of the HPA axis, which can result in adrenal insufficiency [90] (**Fig. 3**).

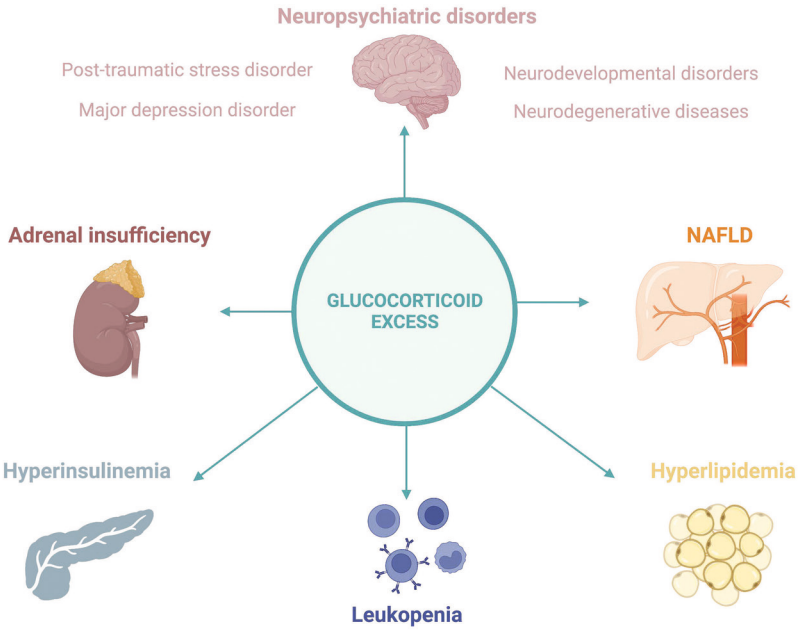

Figure 3. Metabolic and neuropsychiatric disturbances involving the glucocorticoid excess. Abbreviations: NAFLD, non-alcoholic fatty liver disease.

In the brain, disruption in GR signaling as a result of chronic stress or excessive GC exposure, can disrupt neurodevelopment [91, 92], lead to neuropsychiatric disorders, and aggravate neurodegenerative diseases such as Alzheimer's disease [93, 94] (**Fig. 3**). GCs are thought to play an important role in the pathogenesis of post-traumatic stress disorder (PTSD) which can develop in trauma-exposed individuals, with an estimated lifetime prevalence of 6.8% in the United States and 7.4% in the Netherlands before 2010 [95, 96]. More recently, the cross-national prevalence was determined for 24 countries, and the global lifetime PTSD prevalence was 3.9% in the total population and increased to 5.6% in the subset of trauma-exposed individuals [97]. Not all individuals exposed to trauma develop PTSD, suggesting that this pathology is associated with biological vulnerability factors. PTSD is linked to the dysregulation of GR signaling [98, 99], and systematic studies have shown a correlation between PTSD susceptibility and low morning cortisol

levels [100]. Furthermore, a risk allele of *Nr3c1* has recently been associated with lower hair cortisol concentrations and PTSD susceptibility in war veterans (**Fig. 3**) [101].

Depression is the most characterized neuropsychiatric comorbidity in Cushing's syndrome, and studies of major depressive disorder in patients with Cushing's syndrome have reported a prevalence of 50 – 80% [102, 103]. In major depressive disorder, GR-driven negative feedback on the HPA axis is impaired and patients show increased levels of circulating GCs [104, 105]. Depression may be caused by prolonged exposure to stress and GCs. For instance, systemic and inhaled GC medications are correlated with a reduction in white matter integrity, which may lead to adverse neuropsychiatric side effects [106].

The glucocorticoid receptor as a therapeutic target: selectivity and specificity

Considering the variety of metabolic and psychiatric diseases related to alterations in GR signaling, the development of novel therapeutics to target GR is of clinical interest. Mifepristone (RU486) is the predominant GR antagonist used in research and is approved for clinical use. Although surgery remains the first-line treatment for Cushing's syndrome, surgery is not always feasible and is unsuccessful in 20 – 50% of cases [107]. Mifepristone is used to treat patients with Cushing's syndrome in the U.S.A.; but unfortunately, its cross-reactivity with the progesterone receptor makes it less suitable for female patients and the lack of GR selectivity generally increases the risk of adverse side effects [108]. Therefore, a first goal in the development of new GR antagonists is to achieve receptor selectivity, with ligands that have no significant affinity for the MR, or the receptors for progesterone, androgen and estrogens [109]. Such ligands would also be of great benefit to the research community, considering sex dimorphism in stress and GC effects [110–115]. GR agonists have numerous applications mainly due to their anti-inflammatory and immunosuppressive properties. Commonly used GR agonists in clinical practice are prednisone/prednisolone/methylprednisolone, dexamethasone, and betamethasone [116]. Unfortunately, as described in the previous section, excessive activation of the GR causes severe metabolic and neuropsychiatric adverse effects [116–118]. In the case of dexamethasone, the side effects can also be in part attributed to endogenous GC depletion [119–121].

Over the past decade, efforts have been made to develop GR ligands that would retain the beneficial effects of GR activation or inhibition while minimizing adverse side effects. This new category of GR ligands includes "dissociating compounds" that preserve GC anti-inflammatory properties but limit GR-driven transactivation

to only a subset of genes, “soft” steroids with very short half-lives, gene-selective compounds, and selective glucocorticoid receptor modulators [122, 123]. Dissociating ligands typically are aimed to separate transcriptional activation from transcriptional repression, under the assumption that the latter effects are responsible for the therapeutic efficacy [124]. Selective GR modulators are specific in the sense that they target only a subset of gene networks and pathways by inducing a GR conformation that allows distinct GR interactions with downstream signaling factors [109, 125–127].

The ability to modulate the GR interactome results in tissue-, cell-, gene-, and context-specific GR signaling. Selective GR antagonists and selective GR modulators both bear substantial promise in the therapeutic targeting of stress- and GC-related diseases. Beyond their therapeutic value, selective GR antagonists and modulators allow the identification of the molecular mechanisms responsible for the adaptive and maladaptive effects of GCs on metabolic health and brain function.

THESIS OUTLINE

The aim of this thesis is to dissect the underlying genomic and epigenomic mechanisms of GR signaling in metabolic diseases and brain function, and to further characterize the treatment properties of current selective GR antagonists and modulators. In **Chapter 2**, we describe the development of a preclinical pipeline to identify novel selective GR antagonists with beneficial properties in metabolic diseases, from which we identified CORT125329 as the most promising candidate for further clinical evaluation. In **Chapter 3**, we compared the properties of the selective GR antagonist, relacorilant, with those of the clinically used antagonist mifepristone. Relacorilant induced modest disinhibition of the HPA axis compared to mifepristone, which represents a considerable advantage over mifepristone in the treatment of Cushing's syndrome. This effect was associated with lack of GR antagonism in the brain and the absence of classic corepressors in the GR interactome. In **Chapter 4**, we investigated the molecular mechanisms underlying the beneficial effects of the GR modulator CORT118335 in NAFLD and NASH. Our results suggest that the beneficial properties of CORT118335 rely on cell- and gene-specific transcriptional effects and a unique GR interactome that lacks important chromatin remodelers. In **Chapter 5**, we provide an overview of GR and MR actions in the brain and highlight the potential of selective GR targeting in stress-related psychiatric disorders. In **Chapter 6**, we created a gene expression atlas in the mouse hippocampus that recapitulated the cell-specific expression of GR and MR, their target genes, transcriptional coregulators, and the neuropeptides and neurotransmitter receptor repertoire. This study shows the complex cellular heterogeneity of corticosteroid receptor signaling networks in the brain. Finally, in **Chapter 7**, we explored GR signaling in a mouse model of the neurodevelopmental disorder Angelman syndrome, which is characterized by the neuronal absence of the GR interacting protein UBE3A. Our results showed that mice with Angelman syndrome are more sensitive to acute elevations in GC levels and, therefore, are more likely to develop stress maladaptation.

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