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Checks and Balances: the Glucocorticoid Receptor and NF κ B in Good Times and Bad

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Abstract

Mutual regulation and balance between the endocrine and immune systems facilitate an organism's stress response, and are impaired following chronic stress or prolonged immune activation. Concurrent alterations in stress physiology and immunity are increasingly recognized as contributing factors to several stress-linked neuropsychiatric disorders including depression, anxiety, and post-traumatic stress disorder. Accumulating evidence suggests that impaired balance and crosstalk between the glucocorticoid receptor (GR) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) – effectors of the endocrine and immune axes, respectively – may play a key role in mediating the harmful effects of chronic stress on mood and behavior. Here, we first review the molecular mechanisms of GR and NF κ B interactions in health, then describe potential shifts in the GR-NF κ B dynamics in chronic stress conditions within the context of brain circuitry relevant to neuropsychiatric diseases. Furthermore, we discuss developmental influences and sex differences in the regulation of these two transcription factors.

Graphical abstract

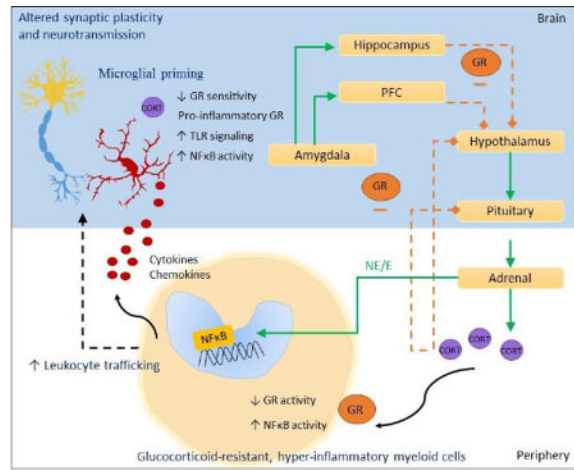
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Declaration of interest

The authors have no conflicting interests.



Keywords

glucocorticoid receptor; nuclear factor kappa-light-chain-enhancer of activated B cells; stress; depression; anxiety; PTSD; FKBP5; inflammation; glucocorticoid resistance

1. Introduction

Balance between the endocrine and immune systems facilitates function of multiple organ systems, and disruption of this balance can precipitate a host of pathologies including neuropsychiatric diseases. Furthermore, due to the highly choreographed interactions among these systems, disruptions in one system quickly spread to the other system. These multifaceted interactions are illustrated by the coordination and cross-talk between the glucocorticoid receptor (GR) within the endocrine system and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) within the immune system. These proteins are transcription factors with a delicate balance of interactions such that alterations in their functions and crosstalk lead to a host of physiological and behavioral changes. The balance between these transcription factors is tested when an organism is exposed to excessive stressor burdens, whether those stressors are environmental or psychological.

Transcription factors such as GR and NF κ B are prime candidates to mediate the impact of wide-scale endocrine and inflammatory dysregulation because of their rapid activation, ability to regulate hundreds of genes at once, and many levels of regulation that allow fine-tuning of their induction and activity. Because of their opposing effects on inflammatory processes, the substantial mutual regulation and crosstalk between GR and NF κ B help shape the effects of stress on the immune system, which in turn, regulates the stress response. During chronic stress, a dysfunctional or less sensitive GR leads to disinhibition of NF κ B-mediated inflammation, and the resulting endocrine-immune imbalance is hypothesized to promote the harmful behavioral and physiological consequences of stress. Beyond the immediate context of inflammation, GR and NF κ B also each independently regulate neurogenesis, synaptic plasticity, and neurotransmission, processes that are thought to contribute to the etiology of neuropsychiatric disorders. This review will focus on GR and NF κ B as a means by which to highlight interactions among the endocrine and immune

systems and detail the repercussions associated with dysfunction of these transcription factors. In order to accomplish this goal, the following areas are addressed:

- 2 Function and Regulation of GR and NF κ B
- 3 Interactions Between GR and NF κ B
- 4 Hallmarks of GR-NF κ B dysfunction
- 5 Traversing the Blood Brain Barrier: from peripheral resistance to central mayhem
- 6 Influence of Age and Sex on GR-NF κ B Interactions

2. Function and Regulation of GR and NF κ B

2.1.1 Structure, Function, and Regulation of GR

The glucocorticoid receptor (GR) is a 777-amino acid nuclear receptor expressed throughout the body (Hollenberg, Weinberger et al. 1985) including the brain (McEwen 1973). The GR is encoded by the *Nr3c1* gene and is responsive to its ligand glucocorticoids (Bell and Munck 1972). As a nuclear receptor, the GR contains a DNA binding domain and a ligand binding domain, both of which are required for nuclear receptor activity (Giguere, Hollenberg et al. 1986). GR resides in the cytosol interacting with a chaperone complex that maintains its activity (Levinson, Baxter et al. 1972, Bresnick, Dalman et al. 1989). Following binding of its glucocorticoid ligand, GR translocates to the nucleus (Davies, Ning et al. 2002) where it interacts with specific DNA sequences called glucocorticoid response elements (GREs). As a transcription factor, GR mediates transcription of numerous target genes involved in a range of actions within an organism including effects on metabolism, reproduction, immunity, and regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Baxter, Rousseau et al. 1972, Rousseau, Higgins et al. 1975, Strahle, Klock et al. 1987, Panagiotakopoulos and Neigh 2014). Glucocorticoids also lead to the eventual resolution of prolonged HPA activity, and suppress their own secretion via binding to GR expressed in regulatory brain regions including the hippocampus, prefrontal cortex, and amygdala. Given the pleiotropic and pervasive effects of GR activation, efficient and effective regulation of receptor activity is essential to organism function and adaptation.

2.1.2 Mechanisms of GR Regulation

Cellular responsiveness to glucocorticoids and activity of the GR can be regulated at multiple levels. The predominant regulatory mechanisms of GR regulation are discussed in the following sections, and an overview of mechanisms of GR regulation is detailed in Figure 1A.

2.1.2a Co-Chaperone Regulation of the GR—As a nuclear receptor, GR resides in the cytosol in a complex with a number of chaperones and co-chaperone proteins. The chaperones and co-chaperones impact function of the receptor, and by modulating the receptor's activity have the ability to impact glucocorticoid signaling. Following translation of the GR protein, GR interacts with the chaperones heat shock protein 90, 70 (Hsp90, Hsp70), and p60 which are required for efficient folding of GR into a conformation with

high-affinity for ligand binding, and interaction with the chaperone p23 further stabilizes the GR-Hsp90 complex (Whitesell and Cook 1996, Dittmar and Pratt 1997). GR resides in the cytosol bound to two molecules of Hsp90, and continued interaction of GR with the chaperone Hsp90 is required to maintain GR's high-affinity conformation (Bresnick, Dalman et al. 1989). In addition to the two molecules of Hsp90, the GR cytosolic complex also contains an immunophilin. The immunophilins FK506 binding protein 51 (FKBP5) and FK506 binding protein 52 (FKBP4) have been widely studied for their regulatory activity of GR and established links to the expression of mood disorders (Binder 2009). FKBP5 and FKBP4 bind to Hsp90 through a tetratricopeptide repeat (TPR) domain. This domain, as well as amino acids in the immunophilin's C-terminal domain, impact the immunophilin's binding affinity to Hsp90 (Silverstein, Galigniana et al. 1999, Cheung-Flynn, Roberts et al. 2003). The GR cytosolic complex consists of two molecules of Hsp90, one molecule of GR, and one immunophilin (FKBP5 or FKBP4). These two proteins, FKBP5 and FKBP4, compete with each other for binding with Hsp90 (Wochnik, Ruegg et al. 2005) and dictate the feasibility of translocation.

Interaction of the GR complex with the immunophilins FKBP5 and FKBP4 have differential action on glucocorticoid signaling. While interaction with FKBP4 facilitates movement of GR to the nucleus, allowing GR to elicit its transcriptional activity, interaction of GR-Hsp90 with FKBP5 inhibits GR-mediated transcriptional activity and efficient translocation of GR to the nucleus. This occurs in part due to reduced interaction of FKBP5 with dynein compared to that of FKBP4 (Wochnik, Ruegg et al. 2005) (Tatro, Everall et al. 2009). When GR interacts with its corticosteroid ligand, the GR-Hsp90 complex dissociates from the co-chaperone FKBP5, and FKBP5 is exchanged for FKBP4. FKBP4 then associates with dynein, a motor protein that assists in nuclear translocation of the GR complex to the nucleus (Davies, Ning et al. 2002). The peptidyl prolyl isomerase (PPIase) domain of FKBP4 is required for association with dynein and movement of the GR complex to the nucleus (Silverstein, Galigniana et al. 1999, Galigniana, Radanyi et al. 2001, Galigniana, Harrell et al. 2002). Dynein then interacts with microtubules to assist in the nuclear transport of GR (Harrell, Murphy et al. 2004). The balance between FKBP5 and FKBP4 in part dictates the extent to which GR can translocate to the nucleus in order to act as a transcription factor.

2.1.2b GR Isoforms—Alternate splicing of GR results in multiple isoforms being expressed, the most commonly studied of which are GR α and GR β . GR α is the traditional GR isoform that mediates transcriptional activity. Alternatively, GR β is primarily located in the nucleus and inhibits GR α transcriptional activity (Oakley, Sar et al. 1996). Multiple sources have cited increased expression of the β isoform as a mechanism of glucocorticoid resistance in inflammatory disease (Leung, Hamid et al. 1997, Honda, Orii et al. 2000, Sousa, Lane et al. 2000, Kozaci, Chernajovsky et al. 2007) due to its ability to inhibit GR α -mediated transcriptional activity. However, the inhibitory activity of GR β on GR α is not universally accepted (Hecht, Carlstedt-Duke et al. 1997), and some cite the relative scarcity of GR β compared to GR α in multiple cell types to argue against the physiological relevance of GR β mediating glucocorticoid resistance (Pujols, Mullol et al. 2002). More recent studies have found that GR β , like GR α , is also able to translocate from the cytosol to the nucleus, a

process that is dependent on Hsp90 and dynein for both isoforms (Zhang, Clark et al. 2006). Furthermore, interaction with immunophilin co-chaperones can also alter GR α and GR β activity such that FKBP5 and FKBP4 have been found to interact with both GR α and GR β (Zhang, Clark et al. 2008), and overexpression of FKBP5 increases nuclear translocation of GR β which reduces transcriptional activity of GR α in the nucleus.

2.1.2c Post-translational Modifications—GR is post-translationally modified on multiple serine residues (Dalman, Sanchez et al. 1988), and can be phosphorylated following glucocorticoid stimuli at these serine residues (Orti, Mendel et al. 1989, Wang, Frederick et al. 2002). Altered patterns of GR phosphorylation can change transcriptional activity of GR. S211 phosphorylation is associated with increased transcriptional activity of GR and a conformational change that may facilitate interaction with cofactors at particular target genes (Wang, Frederick et al. 2002, Chen, Dang et al. 2008). However, this is not a universal effect, and the effect of S211 phosphorylation on gene transcription differs among specific GR target genes (Chen, Dang et al. 2008). Differential phosphorylation patterns of GR result in recruitment of GR to different target genes (Blind and Garabedian 2008) and altered mRNA transcript profiles (Gallagher-Beckley, Williams et al. 2011), providing a mechanism of altering the transcriptional pattern of GR rather than just increased or decreased global activity.

Kinases and phosphatases have been key research tools in elucidating the role of phosphorylation in altering GR-mediated transcriptional patterns. P38 MAPK phosphorylates S211 of GR, and mutation of this site decreases GR's transcriptional activity (Miller, Webb et al. 2005). Conversely, c-Jun N-terminal kinase (JNK) inhibits GR-activity and phosphorylates GR at S246 (Rogatsky, Logan et al. 1998, Szatmary, Garabedian et al. 2004) and S226 (Itoh, Adachi et al. 2002). JNK phosphorylation also increases nuclear export of GR (Itoh, Adachi et al. 2002), and JNK inhibition in HT22 cells dose-dependently increases GR's transcriptional activity (Wang, Wu et al. 2005). This inhibitory activity of JNK-mediated phosphorylation is one mechanism that may contribute to glucocorticoid resistance in a nuanced gene-specific manner.

2.1.2d Receptor Expression and Degradation—Regulation of GR protein expression is an additional mechanism of modulating signaling activity of GR. Glucocorticoid treatment downregulates GR expression in cell models (Cidlowski and Cidlowski 1981, Silva, Powell-Oliver et al. 1994), and chronic corticosterone treatment decreases GR protein in specific brain regions (Hu, Zhang et al. 2016). However, inhibition of proteasomes reverses the effect of glucocorticoid treatment on GR expression, establishing the role of proteasomal degradation in glucocorticoid-mediated regulation of GR protein concentrations. Following treatment with glucocorticoids, the GR can be ubiquitinated, signaling its designation for proteasomal degradation. Changes in GR protein concentrations following glucocorticoid treatment have been found to be functional; reporter gene analysis shows that proteasome inhibition increases dexamethasone-mediated GR transcriptional activity (Wallace and Cidlowski 2001). Degradation of GR has been proposed to be a mechanism of cell-type specific glucocorticoid resistance (Mata-Greenwood, Stewart et al. 2013). Furthermore, interaction with the co-chaperone Bag-1 also promotes GR's degradation (Demand, Alberti

et al. 2001). In dexamethasone-resistant HUVECs, higher levels of Hsp70 recruitment to GR following dexamethasone treatment occurs and increased interaction of GR with Bag-1, and overexpression of Bag1 decreases protein levels of GR (Mata-Greenwood, Stewart et al. 2013).

2.1.2e Glucocorticoid Availability—The previous mechanisms of GR regulation involve direct modulation of GR in terms of availability, function, and structure. Although not as well-delineated at this point, availability of glucocorticoid ligand is also able to modulate GR signaling in the cell. P-glycoprotein expels glucocorticoids from the cell, and reduced activity of this pump may increase intracellular concentration of glucocorticoids, thus increasing activation and subsequent signaling of GR (Pariante, Kim et al. 2003). However, the impact of these cell efflux pumps is disputed. Other studies question the physiological relevance of p-glycoprotein in altering HPA axis responses in rodents (Mason, Pariante et al. 2008). More recently, strain differences or different isoforms of p-glycoprotein have been hypothesized to impact the somewhat conflicting data on the role of p-glycoprotein in modulating GR activity (Mason, Pariante et al. 2012).

2.1.2f GR action during transcription—Binding of GR to the GRE binding site results in dimerization of the DNA binding domain of GR (Luisi, Xu et al. 1991) and increases in gene expression of its target genes (Chandler, Maler et al. 1983). GR is also able to bind to negative GRE (nGRE) DNA binding sequences on which the GR reduces transcriptional activity through interaction with transrepression complexes (Surjit, Ganti et al. 2011). GR binds to nGRE as two separate GR monomers on opposite sides of the DNA strand in an orientation that prevents GR dimerization, a conformation in contrast to GRs at positive GREs where GR binds on the same side of the DNA strand (Hudson, Youn et al. 2013).

2.1.2g Non-genomic actions of GR—Though discussion of GR signaling often concerns transcriptional regulation through the classical GR nuclear receptor, GR also can exert non-genomic effects. Rapid effects have been observed following glucocorticoid stimulation, and these effects occur too quickly to be explained by genomic GR actions through altered transcription. Much research in non-genomic actions of GR has centered around fast feedback inhibition of the HPA axis (Iwasaki, Aoki et al. 1997, Deng, Riquelme et al. 2015), and non-genomic effects of glucocorticoids have been studied in multiple cell types, including cells that mediate immune and inflammatory responses. Membrane-bound GR has been found to be responsible for much of the non-genomic actions of glucocorticoids (Perez, Cormack et al. 2013). Membrane-bound GRs have been found in monocytes, B-cells, T-cells, and neurons (Bartholome, Spies et al. 2004, Lowenberg, Verhaar et al. 2006, Tryc, Spies et al. 2006, Shaqura, Li et al. 2016).

2.2.1 Structure, Function, and Regulation of NF κ B

The family of NF κ B proteins serve as transcription factors that regulate immune and inflammatory responses, cell survival, development, synaptic plasticity, and neurogenesis (Kaltschmidt and Kaltschmidt 2009). NF κ B is present in all cell types (Hoffmann and Baltimore 2006) and due to its prominent role in inflammatory signaling, is extensively studied in many diseases including cancer, rheumatoid arthritis, asthma, cardiovascular and

metabolic disease. NF κ B can be activated by numerous inflammatory, physiological, and cellular stress signals (for a complete list, refer to www.nf-kb.com). When activated, it regulates the transcription of hundreds of target genes relevant to a diverse array of physiological functions. Multiple receptor-specific intracellular transduction pathways such as toll-like receptors (TLRs), TNF- α receptor, IL-1 receptor, T- and B-cell receptor signaling can converge upon the NF κ B pathway. Furthermore, adjacent inflammatory signaling cascades including the p38/MAPK, JNK pathways can interact with and mutually regulate the NF κ B pathway (Oeckinghaus, Hayden et al. 2011).

There are five polypeptides in the NF κ B family that contribute to the diversity of this transcription factor (p65, cRel, Rel, as well as the precursor proteins p100 and p105 that get proteasomally cleaved into the subunits p52 and p50). All five subunits contain a conserved Rel-homology domain, which allows dimerization between subunits and enables DNA-binding. These subunits form 15 possible dimers that display either transcriptional activator, repressor, or no DNA-binding ability depending on dimer composition (Hoffmann and Baltimore 2006). The p65, Rel, and cRel proteins possess a transcriptional activation (TA) domain, which is required for target gene transcription. In contrast, the p50 and p52 subunits do not contain a TA domain, and are unable to regulate gene transcription unless dimerized to another NF κ B subunit that possesses a TA domain. Dimers exclusively composed of p50 or p52 are therefore often referred to as transcriptional repressors. Finally, the p65/Rel, cRel/Rel, and Rel/Rel dimers are unable to bind to DNA.

2.2.2 Canonical and non-canonical NF κ B pathways

Similar to GR, the NF κ B protein complex resides sequestered in the cytoplasm in the absence of relevant stimuli such as cytokines, growth hormones, cellular and oxidative stress, and synaptic transmission. Within NF κ B signaling pathway, there are two distinct cascades, canonical and non-canonical, that are activated by different stimuli and perform different functions. The canonical pathway is activated by pro-inflammatory stimuli including the archetypal pro-inflammatory cytokines TNF- α and IL-1 β as well as microbial products. The canonical pathway mediates rapid immune activation such as that during acute infection. The non-canonical pathway can be activated by both immune (lymphotoxin- β , CD40 ligand, B-cell activating factor) and non-immune stimuli, and is involved in slow and sustained immune regulation such as that which occurs during development of the immune organs. The canonical and non-canonical pathways also differ in the composition of NF κ B. The canonical pathway features the most common form of NF κ B, the heterodimer which consists of p65 and p50. In contrast, the non-canonical pathway features heterodimers containing p52 and Rel proteins.

2.2.3 Molecular Regulation of NF κ B Signaling

In addition to different dimer compositions, the two types of NF κ B signaling cascades have both shared and distinct regulatory features. Due to the dual points of regulation, cytosolic and nuclear, for purposes of organization, we subset regulatory processes by compartment.

2.2.3a. Regulation of NF κ B signaling prior to nuclear translocation—The main regulatory event in both the canonical and non-canonical cascades is the phosphorylation

and subsequent degradation of the inhibitor I κ B proteins by the appropriately-named I κ B kinase (IKK) proteins, thus freeing the NF κ B complex to translocate to the nucleus. In the absence of NF κ B-activating stimuli, the I κ B proteins serve to inhibit nuclear translocation and DNA-binding of NF κ B subunits, and they accomplish this by binding to the Rel-homology domain present on all five NF κ B proteins. There are several forms of I κ B proteins, including I κ B α , I κ B β , I κ B ϵ , and I κ B γ . In addition, the uncleaved precursor proteins p100 and p105 are also considered a type of I κ B proteins because they also contain the Ankyrin repeat domain, a hallmark of I κ B proteins. While I κ B masks the nuclear localization signal on NF κ B when the latter is inactive, I κ B does not completely prevent nuclear translocation. Rather, I κ B is thought to reduce the rate of nuclear translocation of the NF κ B-I κ B complex that is constantly shuttling between the cytoplasm and the nucleus.

NF κ B-activating stimuli trigger the activation of the IKK, which has been described as the core element of NF κ B regulation (Israel 2010). There are two IKK proteins, IKK α and IKK β , and a third regulatory protein IKK γ (also referred to as NEMO). The canonical IKK complex contains a heterodimer of IKK α and IKK β , and is regulated by the scaffold protein IKK γ . In the canonical pathway, the IKK β catalytic subunit phosphorylates I κ B, which is then ubiquitinated and proteasomally degraded, thus freeing the NF κ B dimer to translocate into the nucleus. In contrast, the non-canonical complex contains only the IKK α homodimer and its upstream kinase NIK (Hoffmann and Baltimore 2006). In the non-canonical pathway, IKK α phosphorylates the p100 or p105 subunit, which are then processed into p50 or p52, respectively, getting rid of the inhibitory Ankyrin repeat domain in the cleaving process. Translocation of the newly released NF κ B is mediated via dynein (Mikenberg, Widera et al. 2007) and importin molecules (importin- α) (Fagerlund, Melen et al. 2008) (See Figure 1B).

2.2.3b. Regulation of NF κ B following nuclear translocation—Once in the nucleus, NF κ B binds κ B response elements (κ RE) in the promoters of cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors. Binding of NF κ B to κ RE initiates transcription via recruitment of the basal transcription machinery including RNA Pol II as well as co-factors necessary for transcription such as p300 and CREB binding protein (CBP). All dimers of NF κ B can bind to the κ B response element; however, the expression and activation of each dimer type is highly cell type-, developmental stage- and stimulus-dependent (Hoffmann and Baltimore 2006, Sen and Smale 2010). In addition, NF κ B binding to the promoter has been described to trigger the formation of enhanceosomes, which are nucleoprotein complexes consisting of several cooperating transcription factors, that ensure the spatially- and temporally- specific induction of a gene (Tian and Brasier 2003). Due in part to the extensive redundancy and cross-feedback in inflammatory signaling pathways, different inflammatory transcription factors usually act in concert to yield stimulus-specific activation of each target gene. This is accomplished by varying combinations of transcription factors such as NF κ B, SP-1, IRFs, STATs, CREB, and AP-1 sequentially binding to their respective response elements within an enhancer region of the target gene. Another key determinant of the rate of target gene induction by NF κ B is elements of the promoter architecture such as number and proximity of κ RE present (with greater number of κ RE clustered closely together corresponding to stronger induction).

While many of the target genes induced by NF κ B are pro-inflammatory in nature, and can perpetuate and prolong the NF κ B response, other target genes function to suppress and contain the inflammatory response caused by NF κ B. For example, among the target genes of NF κ B is its negative regulator, I κ B. Newly synthesized I κ B protein retains the NF κ B complex in the cytoplasm and prevents its transcriptional activity, thus creating an ultra-short negative feedback loop on NF κ B activity – similar to that discussed above between GR and FKBP5. Following NF κ B activation, the quantity of total I κ B protein can include both initial I κ B protein that was available prior to NF κ B activation and newly synthesized I κ B post-activation; therefore, researchers distinguish between phosphorylated I κ B amount, which indicates I κ B about to be degraded, and total I κ B protein in the cell.

2.2.3c. Post-translational modifications of the NF κ B pathway—Activation of the IKK proteins, which is necessary for NF κ B induction, has been described to be accomplished by various post-translational events (reviewed in (Perkins 2006)). The most common modifications include the ubiquitination of IKK γ and phosphorylation of IKK α and IKK β . In addition, the TA domain present on p65, Rel, and cRel may be subject to post-translational modifications such as phosphorylation and acetylation for selective induction and optimal regulation of NF κ B. Numerous post-translational modifications of NF κ B have been described in a stimulus- and cell type-specific manner (Perkins 2006). For example, lipopolysaccharide (LPS), a bacterial toxin widely used in research to stimulate NF κ B, signals via TLR4 and then phosphorylates serine 276 on p65 via the catalytic subunit of PKA, whereas several other kinases have been reported to phosphorylate S536 following LPS. Another common post-translational modification of NF κ B is the reversible acetylation of p65 on one of multiple lysine residues by the transcriptional co-activator proteins p300 and CBP, which enhances p65's binding to DNA (Chen, Mu et al. 2002).

Activity of NF κ B can therefore be measured via assessing the 1) availability of IKK proteins that initiate the entire NF κ B cascade, 2) amount of phosphorylated I κ B proteins, 3) degree of post-translational modification of NF κ B subunits specific to stimulus, 4) degree of nuclear translocation or presence of NF κ B subunits, most commonly p65, 5) extent of NF κ B binding to DNA (κ RE), and 6) NF κ B-mediated transcription of its downstream target genes including both endogenous target genes and reporter constructs.

3. Interactions between GR and NF κ B

The mutual regulation and interaction between GR and NF κ B are understood to be highly stimulus-, cell type-, and time course-dependent, and are an ongoing focus of a substantial body of research (see De Bosscher, Vanden Berghe et al. (2003) for review). Under most acute activation scenarios, GR and NF κ B display mutually antagonistic effects, and as such the focus of Section 3 will be details of this two-way negative regulation. However, certain combinations of stimuli, or prolonged activation, can cause GR and NF κ B to exert synergistic effects on a subset of genes (Rao, McCalman et al. 2011), depending on the architecture of GREs and κ REs present on target gene promoters. Furthermore, disruptions to the endocrine-immune balance, such as that which occurs during chronic stress, may also entail synergistic effects between GR and NF κ B, and will be discussed in Section 4.

The crosstalk between GR and NF κ B primarily occurs following nuclear entry (Section 3.2) via several mechanisms most notably among them transrepression and trans-activation. Additionally, interactions between the two pathways in the cytoplasm prior to nuclear translocation have also been documented as detailed in Section 3.1.

3.1 GR-NF κ B interactions at the level of nuclear translocation

As described above, both GR and NF κ B are inducible transcription factors, and their activity is regulated by negative feedback loops involving transcription of their respective inhibitors FKBP5 and I κ B. Both GR and NF κ B reside in the cytoplasm tethered by these negative inhibitor proteins, and nuclear translocation is a required step for function of both. Considerable similarities exist in the mechanisms regulating the nuclear translocation of GR and NF κ B, and several avenues for protein-protein interactions between the two pathways have been described (see Figure 2).

3.1.2 GR effects on I κ B—As detailed previously, NF κ B's rate of nuclear translocation and DNA-binding activity is suppressed by its binding to I κ B proteins. Furthermore, GR increases the binding affinity of I κ B to NF κ B complex (Scheinman, Cogswell et al. 1995). Even in the absence of corticosteroid signaling, cytosolic GR has been shown to interact with p65, p50, and I κ B, and inhibit nuclear translocation of NF κ B (Widen, Gustafsson et al. 2003).

3.1.3 Chaperone Influences—Protein-protein interaction partners of NF κ B and GR overlap substantially, with several key players having been shown to influence the nuclear translocation of each transcription factor primarily *in vitro* (Bouwmeester, Bauch et al. 2004, Hinz, Broemer et al. 2007, Rein 2016). GR is tethered in the cytoplasm by the chaperone Hsp90 and a number of co-chaperone proteins including most notably FKBP5. Emerging evidence indicates that subunits of the NF κ B complex as well proteins constituting the cascade that regulates NF κ B activation are able to interact with various members of the family of chaperone proteins that regulate GR's nuclear translocation, yet the functional significance of these associations *in vivo* remain largely undetermined (Rein 2016). For example, NF κ B has been shown to associate with the cellular stress-inducible heat shock protein 70 (Hsp70) in human T-lymphoma cells (Guzhova, Darieva et al. 1997) and heat shock cognate 70 (Hsc-70), the constitutively expressed form of Hsp70, in hippocampal neurons (Klenke, Widera et al. 2013). While heat shock proteins including Hsp90 and Hsp70 are best known for promoting protein folding, trafficking, and degradation, and along with p23 form the cytoplasmic chaperone machinery that enables GR transport, the latter finding was interpreted to suggest a potential role in axonal transport in neurons.

3.1.4 NF κ B's interactions with FKBP5—The co-chaperone FKBP5, which inhibits the nuclear translocation of GR, and under chronic stress conditions promotes a glucocorticoid-insensitive state (Guidotti, Calabrese et al. 2013), has been reported to interact with many members of the TNF- α -induced NF κ B pathway including TAK1, MEKK1, (Bouwmeester, Bauch et al. 2004), TNF receptor-associated factor-2 (TRAF2) (Romano, Xiao et al. 2015), TRAF3, TRAF6 (Akiyama, Shiraishi et al. 2014), IKK α , IKK ϵ (Bouwmeester, Bauch et al. 2004, Romano, Xiao et al. 2015), IKK β (Romano, Xiao et al. 2015) and p65 (Erlejan, De

Leo et al. 2014), with conflicting reports of its impact on overall NF κ B activity. Whereas siRNA-mediated knockdown of FKBP5 was found to decrease the nuclear translocation of p65 in MEF cells (Akiyama, Shiraishi et al. 2014) and suppress NF κ B reporter activity in HEK293 cells (Bouwmeester, Bauch et al. 2004), another study found that FKBP5 downregulation had no impact on either I κ B degradation or p65 translocation (Hinz, Broemer et al. 2007). In contrast, one study reported that overexpression of FKBP5 prevented, whereas that of FKBP4 facilitated, the nuclear translocation of NF κ B in HEK293 cells, resembling the co-chaperones' well-described regulation of GR (Erlejman, De Leo et al. 2014). Although it is unclear in some of these reports whether the impact of FKBP5 on NF κ B activity is mediated via direct protein-protein interactions or via FKBP5's regulation of GR, taken together these reports raise the intriguing possibility that co-chaperone-regulated nuclear translocation may represent a previously unexamined checkpoint for GR and NF κ B balance. As indicated above, FKBP5's involvement in NF κ B pathway has been studied in the context of oncology because of its overexpression in some types of cancer (Jiang, Cazacu et al. 2008, Romano, Mallardo et al. 2011); however, despite the abundant knowledge of FKBP5's impact on the activity of GR in the context of endocrine disruptions, and the established potent anti-inflammatory properties of GR, little work has investigated FKBP5's role in chronic stress-induced inflammation.

3.1.5 Beyond protein-protein interactions—Beyond shared protein-protein interaction partners, several other mechanisms have been described to influence GR and NF κ B regulation. The catalytic subunit of protein kinase A (PKAc) which phosphorylates p65 attenuates the mutual antagonism between GR and NF κ B (Doucas, Shi et al. 2000). Patients with major depression may be particularly vulnerable to the anti-glucocorticoid effects of inflammatory cytokines due to the decreased PKA signaling activity (a pathway that promotes GR activity that decreases the inhibitory activity of cytokines IFN α on GR) (Shelton, Sanders-Bush et al. 2009, Pace, Hu et al. 2011). Activation of the cAMP/PKA pathway through use of forskolin attenuates IFN α -mediated inhibition on GR, and inhibition of PKA impairs GR transcriptional activity (Pace, Hu et al. 2011). The disinhibition of GR signaling by PKA may be mediated by PKA's inhibitory effects on NF κ B (Gao, Hibi et al. 2010, Pace, Hu et al. 2011). Activation of cAMP/PKA also impairs activity of pSTAT5, an inhibitor of GR, which could contribute to enhanced GR activity (Pace, Hu et al. 2011).

3.2 GR-NF κ B interactions at the transcriptional level

Mutual antagonism between GR and NF κ B has been described to occur via several well-defined mechanisms including transrepression (*e.g.* repression of pro-inflammatory NF κ B targets by GR), trans-activation (*e.g.* activation of NF κ B inhibitor genes by GR), and competition for co-factors and co-activator proteins necessary for transcriptional activity as detailed below (see Figure 3). It should be noted that considerable redundancies exist between inflammatory signaling pathways, and components of one pathway can often compensate the loss of another pathway's functional effectiveness, and conversely, glucocorticoid-mediated suppression of parallel pathways such as the MAPK pathway can also diminish NF κ B activation (see Clark (2003) for review). As such, the GR signaling pathway not only cross-regulates NF κ B but also similar inflammatory pathways including TNF- α (Van Bogaert, De Bosscher et al. 2010).

3.2.1 Transrepression—The mechanism of interaction between GR and NF κ B has been extensively studied, and the GR has been found to interact with NF κ B through direct protein-protein interactions that impair NF κ B transactivation (De Bosscher, Schmitz et al. 1997). The precise nature of the interaction between GR and NF κ B is gene-specific (De Bosscher, Vanden Berghe et al. 2003). GR physically interacts with p65, and decreased transcriptional activity of NF κ B at the IL-6 promoter occurs with dexamethasone treatment (Ray and Prefontaine 1994). Dexamethasone also decreases IL-8 transcription through inhibiting NF κ B's transcriptional activity. These studies determined that dexamethasone's inhibitory activity on IL-8 transcription does not depend on decreased nuclear translocation of NF κ B but through blocking the binding of NF κ B to the DNA (Mukaida, Morita et al. 1994). However, other studies examining transrepression of additional NF κ B genes such as IL-6 do not require impaired DNA binding of NF κ B to elicit reduced gene expression but rather argue that GR impairs transactivation of p65 through altered interaction with basal transcriptional machinery (De Bosscher, Schmitz et al. 1997, De Bosscher, Vanden Berghe et al. 2000). The GR can also interact with p50, resulting in impaired transcriptional activity of NF κ B. Interactions of the GR with p65 and p50 require the zinc finger domain of GR (Scheinman, Gualberto et al. 1995).

The interaction of GR and NF κ B is not one-sided in transrepressive activity. P65 also inhibits GR activity at glucocorticoid response elements (Scheinman, Gualberto et al. 1995), and GR-mediated transcription of specific target genes is dose-dependently decreased through overexpression of p65 (Waltner-Law, Daniels et al. 2000). This inhibition occurs through two amino acids in the C-terminal zinc finger of the DNA binding domain of GR (Liden, Delaunay et al. 1997). Though the earliest understanding of GR-NF κ B interactions is that activity of one only reduces activity of the other, more recent studies have identified that GR and NF κ B can have synergistic effects or stimulatory effects on transcription of the other at specific genes (Lamirand, Ramaugue et al. 2011).

3.2.2 Trans-activation of anti-inflammatory targets and upregulation of I κ B by GR—Although much of GR's suppression of NF κ B is mediated by transrepression mechanisms, a substantial body of evidence also suggests that trans-activation of anti-inflammatory genes by GR also contributes to inflammatory suppression (Newton and Holden 2007). For example, transcription of MKP-1, a kinase that negatively regulates the p38 MAPK pathway (and by extension the NF κ B pathway), has been demonstrated to be strongly glucocorticoid-responsive (Lasa, Abraham et al. 2002). Interestingly, the expression of anti-inflammatory genes normally transcribed by NF κ B as part of a negative feedback regulation (including TNFAIP and NFKBIA) were found to be spared from suppression by GR, unlike many pro-inflammatory target genes of NF κ B (Altonsy, Sasse et al. 2014). These studies suggest that GR's anti-inflammatory effects on NF κ B are nuanced and employ highly specific mechanisms depending on the promoter architecture and function of each target gene. Furthermore, early studies indicated that dexamethasone-activated GR can transcribe I κ B, resulting in newly synthesized I κ B protein that can quickly associate with NF κ B and inhibit the latter's nuclear translocation (Scheinman, Cogswell et al. 1995). However, I κ B upregulation by GR is unlikely to be the primary mechanism of glucocorticoid-mediated suppression of inflammation because NF κ B suppression by GR

still occurs in the absence of trans-activation by GR (De Bosscher, Vanden Berghe et al. 2003).

3.2.3 Competition for co-activators—Upon translocation to the nucleus, both GR and NF κ B interact with the co-activators CBP and steroid receptor coactivator-1 (SRC-1). Some studies demonstrate that competition for these coactivators may also contribute to the mutual antagonism between GR and NF κ B (Sheppard, Phelps et al. 1998) though other studies disagree with the limiting potential of CBP (De Bosscher, Vanden Berghe et al. 2000, McKay and Cidlowski 2000). And finally, in addition to transrepressing NF κ B activity, GR may also increase nuclear export of NF κ B (Nelson, Wilde et al. 2003) and specifically by exporting p65 following treatment with dexamethasone (Scheinman, Gualberto et al. 1995).

3.2.4 Influence of GR Receptor Subtype on NF κ B—As discussed in Section 2.1.2b, there are two isoforms of GR. Differences between GR α and GR β may play a role in the interactions between GR and NF κ B signaling in the cell. For example, cytokine-induced NF κ B transcriptional activity has been demonstrated to increase the expression of GR β relative to GR α (Webster, Oakley et al. 2001). The increased GR β protein driven by cytokine signaling may mediate glucocorticoid resistance and correlated with GR β protein increases (Webster, Oakley et al. 2001). Furthermore disinhibition may occur by interactions between GRs, such that, GR β can diminish GR α -mediated inhibition of NF κ B (Oakley, Jewell et al. 1999).

3.2.5 Influence of non-genomic GR on NF κ B—Anti-inflammatory effects of glucocorticoids have been observed rapidly following stimulation. These rapid anti-inflammatory effects following glucocorticoid stimulation have been attributed to the non-genomic activity of glucocorticoids rather than through GR's genomic actions (Lowenberg, Tuynman et al. 2005, Lowenberg, Verhaar et al. 2006). Non-genomic glucocorticoid effects have been detected in immune cells (Long, Wang et al. 2005, Lowenberg, Verhaar et al. 2006). Furthermore, non-genomic effects of glucocorticoids may also alter multiple downstream signaling pathways including the proteins p38 MAPK, JNK, protein kinase C, protein kinase A, and ERK1/2 (Qiu, Wang et al. 2001, Solito, Mulla et al. 2003, Lowenberg, Tuynman et al. 2005, Qi, Qiu et al. 2005, Verriere, Hynes et al. 2005, Roy and Rai 2009). As discussed in previous sections, signaling through p38 MAPK, JNK, and PKA can have modulatory effects on NF κ B, and non-genomic effects of glucocorticoids on these signaling proteins could be another mechanism through which GR signaling impacts NF κ B and inflammation.

4. Hallmarks of GR- NF κ B Dysfunction?

4.1 Glucocorticoid Resistance

Prolonged exposure to glucocorticoids, such as during chronic stress, has the capacity to lead to glucocorticoid resistance, which broadly refers to decreased glucocorticoid signaling due to impaired activity of GR. Even the terminology, glucocorticoid resistance, has taken on a dual identity reflecting an impact within both the endocrine and immune systems. Within the chronic stress literature, glucocorticoid resistance primarily indicates *impaired*

negative feedback regulation of the stress axis – which is mediated by GR – culminating in increased cortisol availability. In the context of chronic inflammatory disorders, glucocorticoid resistance indicates *diminished ability of glucocorticoids to suppress inflammatory processes* such as release of cytokines, proliferation of immune cells and receptors, or at high concentrations, to trigger apoptosis (Barnes and Adcock 2009).

We focus here on chronic stress-related mood disorders because they represent a multidimensional sum of the two forms of glucocorticoid resistance with increased glucocorticoid levels and a less transcriptionally active GR (Pace, Hu et al. 2007), coupled with greater activation of innate immunity in the brain and the body that may be further exacerbated by glucocorticoids (Frank, Thompson et al. 2012, Sorrells, Munhoz et al. 2014). Perhaps even more salient than individual alterations in GR or NF κ B is the impaired balance and crosstalk between GR and NF κ B. In healthy systems, the crosstalk and balance between GR and NF κ B activity are precisely coordinated and regulated (Adcock and Barnes 2008). Following acute psychosocial stressors in healthy humans, NF κ B activity in peripheral immune cells peaks within 20 minutes (Bierhaus, Wolf et al. 2003, Wolf, Rohleder et al. 2009, Kuebler, Zuccarella-Hackl et al. 2015), and the subsequent activation of the HPA axis – including the release of adrenocorticotropic hormone (ACTH) and cortisol which peaks by 30–40 minutes following onset of stressor (Bierhaus, Wolf et al. 2003, Kuebler, Zuccarella-Hackl et al. 2015) – serves to suppress this NF κ B-driven inflammation. However, evidence demonstrates that in disease conditions not only is GR unable to adequately suppress NF κ B activity but also the resulting excessive NF κ B leads to further impairment of GR's anti-inflammatory function, thus setting in motion a vicious circle of GR-NF κ B imbalance (Pace, Hu et al. 2007). In the context of mood disorders, excessive or inappropriate activation of NF κ B within both peripheral immune cells and directly in the brain plays a key role in initiating and sustaining stress-induced neuroinflammation, as well as structural and behavioral deficits (Munhoz, Lepsch et al. 2006, Koo, Russo et al. 2010).

Much of the human evidence implicating concurrent dysregulation of GR and NF κ B in psychiatric illnesses is derived from blood cell samples from patients with mood disorders or chronically stressed populations. These studies indicate a transcriptional fingerprint characterized by reduced GR- and increased NF κ B-mediated transcription (Miller, Chen et al. 2008, Miller, Murphy et al. 2014). For example, healthy adult parents who were caregivers to pediatric cancer patients displayed reduced morning cortisol levels compared to parents of healthy children, and had a reduced ability of dexamethasone to suppress IL-6, but not TNF α or IL-1 β production (Miller, Cohen et al. 2002). Adolescent female subjects with higher chronic interpersonal stress displayed greater increases in NF κ B, GR β , and I κ B mRNA in leukocytes over a six month period, and exhibited higher LPS-stimulated IL-6 expression compared to subjects with lower interpersonal stress (Miller, Rohleder et al. 2009), suggesting glucocorticoid resistance. Greater NF κ B DNA-binding concurrent with blunted glucocorticoid sensitivity has been reported in women with childhood abuse-related post-traumatic stress disorder (PTSD) (Pace, Wingenfeld et al. 2012). Diminished suppression of inflammation by cortisol in monocytes was associated with increased depressive mood in patients (Cheng, Dimitrov et al. 2016). Conversely, cognitive-behavioral stress management has been found to reverse anxiety-related upregulation of pro-inflammatory transcripts in leukocytes of women undergoing breast cancer treatment

(Antoni, Lutgendorf et al. 2012). Specifically, transcripts that were upregulated by cognitive-behavioral stress management were found to have an underrepresentation of the κ B response element in the promoter and an overrepresentation of GREs, suggesting decreased transcriptional activity at κ RE coupled with increased activity at GREs (Antoni, Lutgendorf et al. 2012). Similarly, practicing yogic meditation was found to reverse NF κ B and interferon regulatory factor (IRF)-related transcriptome in leukocytes of caregivers (Black, Cole et al. 2013). Cumulatively, these findings strongly implicate the concurrent dysfunction and imbalance of GR and NF κ B in stress-related psychiatric illnesses and associated glucocorticoid resistance.

4.2 Potential Mechanisms of Glucocorticoid Resistance

Several mechanisms by which chronic stress could lead to decreased GR and increased NF κ B activity are possible (see Figure 4). First, co-chaperone variations could drive altered interactions between GR and NF κ B as suggested by polymorphisms of the FKBP5 gene which have been associated with increased incidence of depressive episodes in humans and altered response to antidepressant treatment (Binder, Salyakina et al. 2004). Altered FKBP5 protein levels in the frontal cortex, indicative of GR dysregulation, have also been found in the frontal cortex of subjects with major depressive disorder (Tatro, Everall et al. 2009). Interestingly, microRNAs (miRNA) that are predicted to interact with GR and FKBP5 have also been implicated as potential variables in altered glucocorticoid responsiveness in rodent models of stress-induced disorders (Jung, Wang et al. 2015). Altered phosphorylation of GR may be another mechanism through which glucocorticoid and inflammatory systems achieve balance. IL-2 and IL-4 decrease GR phosphorylation (Pazdrak, Straub et al. 2016), and phosphorylation of GR impacts its ability to interact and transrepress NF κ B (Gallagher-Beckley, Williams et al. 2008). To this end, patients with depression exhibited higher cortisol levels that correlated with S226 phosphorylation of GR (Simic, Maric et al. 2013). Nuclear expression of GR phosphorylated at S226 in leukocytes also correlated with self-reported current depression in women, and this effect was absent in men (Simic, Adzic et al. 2013).

Finally, it has recently been proposed that when dysfunctional, glucocorticoids not only signal less effectively, but also exert a pro-inflammatory impact when they do (Horowitz and Zunszain 2015). In particular, glucocorticoid signaling has been demonstrated to enhance inflammation under both stress (Frank, Thompson et al. 2012) and conditions of central nervous system injury (Sorrells, Caso et al. 2009). One potential mechanism through which glucocorticoids may act in a pro-inflammatory fashion is through changes to stimulus specificity of GR and NF κ B. For example, when cells from steroid resistant but otherwise healthy individuals were stimulated with dexamethasone, the expected increase in GR DNA-binding was absent and increased NF κ B DNA-binding was found to occur (Dawson, Dhanda et al. 2012). Other molecular mechanisms of glucocorticoid-immune imbalance are discussed within the context of specific brain regions in the next section.

5. Traversing the Blood Brain Barrier: from peripheral resistance to central mayhem

5.1 Expression and interaction of GR and NF κ B in the brain

In the rat brain, GR is expressed in highest density in the hippocampus (lateral septum and the dentate gyrus), and to a lesser extent in the nucleus tractus solitarii, amygdala (Reul and de Kloet 1985), and hypothalamus. GR is expressed in both neurons and glia. Glial GR is involved in microglial development and proliferation, and is thought to perform crucial anti-inflammatory functions during CNS inflammation and provides neuroprotection (Carrillo-de Sauvage, Maatouk et al. 2013). However, under certain conditions characterized by stress or injury, glucocorticoids can prime hippocampal microglia to assume a more pro-inflammatory profile (Frank, Baratta et al. 2007, Frank, Thompson et al. 2012). This will be further discussed in Section 5.2.

Constitutive NF κ B activity has been demonstrated in several brain regions including the hypothalamus, cortex, hippocampus, amygdala, olfactory lobes, and cerebellum (Schmidt-Ullrich, Memet et al. 1996, Bhakar, Tannis et al. 2002). During systemic inflammation, brain regions most accessible to cerebrospinal fluid (CSF) and blood including the circumventricular organs, and neighboring regions as well as elements of the brain microvasculature and blood-brain barrier (BBB) are likely to express the greatest extent of NF κ B activation owing to the soluble pro-inflammatory factors present in the CSF and blood (Rivest 2001). NF κ B is likely primarily active in the immunocompetent cells of the CNS including microglia due to the widespread expression of immune receptors on these cells. However, NF κ B is expressed in neurons, and is thought to play roles in synaptic plasticity, brain development (Boersma, Dresselhaus et al. 2011), synaptic signaling (Meffert, Chang et al. 2003). Conflicting views exist regarding the origin of NF κ B activity in neurons. Whereas some groups have found minimal NF κ B activity in primary neuronal cultures (Listwak, Rathore et al. 2013, Mao, Phanavanh et al. 2016) others have found constitutive NF κ B activity in neurons (Kaltschmidt, Kaltschmidt et al. 1994, Bhakar, Tannis et al. 2002), and the discrepancy is thought by some to result from varying degrees of purity of neuronal cultures due to mixed glial populations (Barger & Mao, 2012). It has been suggested that NF κ B signaling in glia mediates pathological pro-inflammatory processes whereas signaling within neurons promotes their survival (Camandola and Mattson 2007).

GR and NF κ B interactions have been documented in murine brain cells. Dexamethasone has been shown to suppress the expression of NF κ B target cytokines such as IL-1 β (Minami, Kuraishi et al. 1990), IL-6 (Benveniste, Sparacio et al. 1990) and TNF α (Brenner, Yamin et al. 1993) in mouse brain cells. Conversely, activation of NF κ B in mouse hypothalamic cultures has been demonstrated to suppress dexamethasone-induced genes (Hagimoto, Arima et al. 2013). Though many of the early studies examining transcriptional level interactions of the GR and NF κ B were performed *in vitro*, interactions of GR and NF κ B have been confirmed in the brain using rodent models as well. For instance, glucocorticoids have been shown to decrease binding of NF κ B to DNA (Unlap and Jope 1997, Chantong, Kratschmar et al. 2012) in the rat brain. Evidence of GR-NF κ B interactions in the brain have also been provided by demonstrations of co-immunoprecipitation of the two proteins (Ros-

Bernal, Hunot et al. 2011). In addition, adrenalectomy increases NF κ B-DNA binding in the cortex and hippocampus, supporting GR's inhibitory role on NF κ B activity (Unlap and Jope 1995).

5.2 Chronic-stress induced neuroinflammation

A convincing body of evidence suggests that stress-induced inflammation contributes to the harmful effects of chronic stress on mood and behavior (Padgett and Glaser 2003). Yet, the means by which chronic psychosocial stress leads to inflammation in the brain remains incompletely understood. Due to its central role in regulating innate immunity, NF κ B is positioned to serve critical roles in several mechanisms of stress-induced neuroinflammation as detailed below.

During stress, catecholamine signaling in peripheral immune cells leads to NF κ B activation (Bierhaus, Wolf et al. 2003), resulting in secretion of soluble inflammatory molecules such as cytokines, chemokines, and acute phase proteins. Peripherally released inflammatory molecules can access the brain via several routes including the transport across the BBB, activation of perivascular macrophages and endothelial cells, and the efferent vagus nerve (Dantzer, O'Connor et al. 2008). Prolonged inflammation such as that occurs in chronic stress has been documented to alter permeability of the BBB and promote increased extravasation of soluble factors. In addition to the peripherally-originated soluble signaling molecules, immune cells themselves can infiltrate the brain, and traffic to sites expressing increased chemokine receptors following repeated social defeat (Wohleb, Powell et al. 2013).

Subsequent to the sympathetic nervous system (SNS)-triggered activation of the immune response, the HPA axis is activated either via catecholamine signaling or cytokine signaling (Pace, Hu et al. 2007). Although the effects of GR are commonly conceptualized as anti-inflammatory, there are several contexts in which GR has been documented to enhance pro-inflammatory processes. In particular, timing of glucocorticoid release has been proposed as a key determinant of this shift (Dhabhar 2009, Horowitz and Zunszain 2015) in which glucocorticoid presence preceding the onset of immune activation has a priming or stimulatory effect, whereas glucocorticoid release that follows immune activation exerts a suppressing effect on inflammation (Frank, Miguel et al. 2010). In fact, glucocorticoids released by both acute inescapable shock stress (Frank, Thompson et al. 2012) or their acute and chronic exogenous administration (Frank, Miguel et al. 2010, Frank, Hershman et al. 2014) sensitize the central and peripheral inflammatory response. Furthermore, in mice experiencing seizures or ischemia glucocorticoid signaling can promote inflammatory processes, including NF κ B activation, in the CNS, and perpetuate tissue damage (Sorrells, Caso et al. 2013, Sorrells, Munhoz et al. 2014).

Stress appears to derail neuroimmune processes by utilizing the immune cells in the brain such as microglia as well as peripheral myeloid cells, and tapping into existing mechanisms that signal cellular stress. In the absence of overt inflammation in the central nervous system (CNS), stress is capable of activating inflammatory signaling pathways via release of danger/damage-associated molecular patterns (DAMPs) and microbe-associated molecular patterns (MAMPs) that bind to immune receptors, a process termed "sterile inflammation"

(Fleshner 2013, Slavich and Irwin 2014). High mobility group box 1 (HMGB1), one of the best-characterized DAMPs, resides undetected in the nucleus of a cell when unstimulated but is released upon activation as demonstrated in a rodent model of inescapable footshock stress (Cheng, Pardo et al. 2016). The released HMGB1 protein can signal through toll-like receptors (TLRs) present primarily on microglia to activate these cells and further promote the spread of inflammation in the brain via NF κ B signaling (Weber, Frank et al. 2015, Cheng, Pardo et al. 2016). In fact, TLR2 and TLR4 signaling within microglia has been demonstrated to be one mechanism underlying the immune-priming effect of glucocorticoids (Frank, Miguel et al. 2010, Weber, Frank et al. 2013). Activation of NF κ B via HMGB1 can also induce the inflammasome-associated protein NLRP3 (nod-like receptor protein 3), which has been implicated in microglial priming by stress and behavioral deficits due to chronic stress (Weber, Frank et al. 2015). In addition to causing the above-mentioned changes in microglia, stress can also prime peripheral immune cells such as splenic monocytes to become glucocorticoid resistant and hyper-inflammatory (Quan 2003). The release and trafficking of these primed cells to the brain have been shown to underlie subsequent anxiety-like behavior both at baseline (Wohleb, Powell et al. 2013) and when re-exposed to a subthreshold stressor (McKim, Patterson et al. 2016).

It should be noted that the majority of the studies examining NF κ B activation in the brain use pro-inflammatory stimuli such as LPS that induce the canonical NF κ B pathway. However, there is some evidence that the non-canonical NF κ B pathway may be involved in affective-like behavior. Kassed and Herkenham (2004) demonstrated that mice deficient in the p50 subunit of the NF κ B complex (thus deficient in non-canonical signaling) show reduced anxiety-like behaviors in tests of exploratory drive and anxiety. A number of alterations in GR and NF κ B systems have been described in various rodent stress paradigms with a particular focus on the hippocampus and prefrontal cortex (PFC), regions involved in the regulation of the HPA axis. These findings are summarized below in 5.3.

5.3 Brain Region-Specific Changes in GR and NF κ B Signaling

5.3.1 Prefrontal Cortex—Several studies to date have reported induction of NF κ B in the PFC following psychosocial stress in rodent models. For example, Madrigal, Moro et al. (2001) found that restraint stress lasting four, but not two, hours led to an increase in nuclear translocation of the p50/p65 NF κ B complex. Increased TNF- α signaling in the brain following immobilization stress has been demonstrated to induce NF κ B-mediated release of inducible nitric oxide synthase (iNOS) which mediates neurotoxic damage (Madrigal, Moro et al. 2001, Madrigal, Hurtado et al. 2002) and accounts for at least one mechanism by which peripheral inflammation can translate into neuronal dysfunction. Furthermore, repeated exposure to combined restraint and acoustic stress led to the activation of the TLR4 pathway in the PFC of mice, and a functional mutation in the TLR4 gene abolished the stress-induced increase in p65 as well as iNOS and COX-2 (Garate, Garcia-Bueno et al. 2013).

Although the functional and behavioral consequences of chronic stress are thought to rest upon the balance between pro- and anti-inflammatory signaling, few studies have examined both GR and NF κ B concurrently. The ratio of GR to NF κ B signaling may be a mechanism

through which environmental stressors impact activity of brain regions involved in the stress response. Hu, Zhang et al. (2016) reported that chronic treatment of mice with dexamethasone for 21 and 28 days decreased the mRNA and protein expression of GR, and increased NF κ B expression in the PFC and hippocampus, and that the net result of increased inflammation may drive the decrease in motor and exploratory behavior and neurodegeneration reported in these mice. Another study found that acute immobilization stress, and to a lesser degree, chronic isolation stress, increased the nuclear ratio of GR to NF κ B protein expression in the rat PFC, (Djordjevic, Adzic et al. 2010) along with evidence of pro-apoptotic signaling. However, nuclear level of NF κ B was unchanged in chronically stressed rats, suggesting that changes to the NF κ B signaling system as a result of chronic stress may not be evident at baseline and that it may take an additional immune stressor to reveal any priming effects of chronic stress to NF κ B.

Consistent with this idea, evidence suggests that chronic stress primes the NF κ B pathway in the brain including in the PFC to a subsequent immune challenge. Rats subjected to chronic unpredictable stress did not differ from non-stressed littermates in basal NF κ B DNA binding, but upon a systemic LPS probe were found to display exaggerated NF κ B DNA binding in the PFC and hippocampus (Munhoz, Lepsch et al. 2006). Interestingly, this stress-mediated NF κ B priming was attenuated by GR inhibition, suggesting an unexpected facilitative role of GR in these regions on the inflammatory consequences of chronic stress exposure (Munhoz, Lepsch et al. 2006). Similar findings were reported by de Pablos, Villaran et al. (2006) who found exaggerated TNF- α induction in the PFC following chronic stress and an intracortical LPS challenge. Likewise, this effect was successfully attenuated with pharmacological inhibition of GR with RU486. Collectively, evidence in the PFC suggests that both baseline and induced expression of NF κ B is potentiated by stress, and that these findings are also accompanied by signs of decreased GR signaling and a shift to pro-inflammatory impact of GR.

5.3.2 Hippocampus—The hippocampus has continued to be a primary focus of chronic stress studies given its vulnerability to both stress and inflammation. The intricate mechanisms that regulate both GR and NF κ B likely contribute to the variability in outcomes such that timing, type of stress, organism selection, and endpoint tissue likely dictate the specific response. Exposure to 21 days of chronic restraint stress has been shown to increase the expression of NF κ B pathway proteins including I κ B, p65, p50 both at baseline and also upon a novel acute stressor (Gray, Rubin et al. 2014). Interestingly, the chronic restraint-induced increase in p50 persisted even after a 21-day recovery, potentially suggesting a role for the p50-mediated non-canonical NF κ B pathway in mediating the lasting impact of chronic stress. Hippocampal NF κ B activity has also been demonstrated to underlie behavioral deficits in a PTSD model where mice experienced a single exposure to predator odor (Cohen, Kozlovsky et al. 2011). The prevalence of extreme behavioral responders was diminished by both a systemic administration of high-dose corticosterone and pyrrolidine dithiocarbamate, a selective NF κ B inhibitor (Cohen, Kozlovsky et al. 2011). Many of the findings of altered GR-NF κ B dynamics previously discussed with regards to the PFC have also been reported in the hippocampus, including stress-induced NF κ B priming (Munhoz, Lepsch et al. 2006), lower GR-to-NF κ B nuclear ratio due to chronic isolation stress

(Djordjevic, Adzic et al. 2009), and chronic dexamethasone-induced decrease in GR and increase in NF κ B (Hu, Zhang et al. 2016). In particular, hippocampal microglia have been demonstrated to underlie the altered endocrine-immune balance in stressed rodents (Frank, Baratta et al. 2007). However, it is important to be mindful of the dramatic variability in chronic stress paradigms which has produced conflicting evidence regarding the impact of chronic stress on NF κ B activity and function. In particular, stress paradigms of either considerable severity or long duration may suppress the immune system, thus potentially leading to conflicting findings regarding NF κ B activity. By way of example, in a sensory contact model in which subordinate mice bred for long attack latency (LAL) live with highly aggressive, dominant mice bred for short attack latency (SAL), separated by a perforated transparent partition for 25 days, NF κ B pathway genes were found to be downregulated in the hippocampus of LAL mice (Feldker, Morsink et al. 2006). Similarly, daily administration of corticosterone to rats for 60 days did not cause hippocampal NF κ B activation despite causing behavioral deficits (Plaschke, Feindt et al. 2006).

Although ample evidence of changes in GR and NF κ B signaling in chronic stress or immune alteration models exists, the functional implications of such changes remain incompletely understood. Differential activity and balance between these two transcription factors may impact function of brain circuitry important in mood and behavior. To this end, hippocampal increases in NF κ B signaling was found to mediate the pro-depressive actions of four weeks of CUS through suppressing adult neurogenesis and altering the ratio of neural stem-like cells (Koo, Russo et al. 2010). Furthermore, rats exposed to chronic social isolation have increased NF κ B to GR ratio in the hippocampus and increased cytosolic Bcl-2, an initiation step of apoptosis (Djordjevic, Adzic et al. 2009). The interactions of GR and NF κ B may be particularly salient. In addition to effects of glucocorticoids on neurogenesis, hippocampal structure, and cell viability (Behl, Lezoualc'h et al. 1997, Zhang, Pan et al. 2016), synthetic glucocorticoid treatment impairs NF κ B DNA binding activity in hippocampal cells and subsequently impairs NF κ B mediated transcription. This additional impairment may facilitate a second and compounding pathway of alterations given that impaired NF κ B transcriptional activity increases susceptibility to oxidative stress induced cell death (Braun, Liebetrau et al. 2000). However, the effects of impairment and stimulation are not simple and bivalent. For instance, the glucocorticoid-expressed kinase SGK1 has been found to increase the formation of spatial memory (water maze) through increasing phosphorylation of IKK α which increases hippocampal NF κ B activity (Tai, Su et al. 2009). Together it is still unclear specifically what balance between GR and NF κ B promotes healthy regulation vs disease, but these studies do implicate alterations in signaling of the two proteins both as a consequence of stress or chronic glucocorticoid exposure, but additional study is necessary to fully elucidate the factors that determine the nature and implications of the interactions of these transcription factors in the hippocampus.

5.4 Synaptic Plasticity

Various forms of chronic stress have been demonstrated to alter the structure and plasticity of synapses. In general, chronic stress has been associated with dendritic atrophy and retraction (Conrad 2008), region-specific alterations in dendritic spine density (see Christoffel, Golden et al. (2011) for review) and reduced long term potentiation (LTP) that

were reversible by anti-glucocorticoid treatment (Krugers, Goltstein et al. 2006). While the role of stress and glucocorticoid-mediated structural and synaptic changes have been intensely studied, the role of NF κ B in synaptic signaling and architecture has only recently been recognized (Kaltschmidt, Widera et al. 2005). It is possible that the effect of chronic stress on plasticity is partially mediated by a stress-induced increase in NF κ B activity. In fact, NF κ B and I κ B were found to localize in the postsynaptic densities and dendritic spines in the rat hippocampus and PFC (Suzuki, Mitake et al. 1997). NF κ B is triggered by synaptic activation (Meffert, Chang et al. 2003) and upon termination of synaptic signal is transported from the synapse back to the nucleus of neurons via a dynein/dynactin motor complex (Widera, Klenke et al. 2016). Furthermore, NF κ B signaling was found to serve as a link between nerve growth factor (NGF) signaling and Notch-dependent gene transcription to mediate neurite growth in hippocampal neurons (Salama-Cohen, Arevalo et al. 2005).

Altered NF κ B activity has been implicated in chronic stress-induced synaptic alterations in the nucleus accumbens (NAc), a region that is involved in anhedonia, one of the core symptoms of depression. However, the functional implications of NF κ B induction by stress appears to vary according to stressor type and duration, as well as the sex of the animal. On one hand, NF κ B signaling in the NAc has been shown to protect against the pro-depressive effects of six days of chronic unpredictable stress (CUS) in ovariectomized female mice compared to intact females (LaPlant, Chakravarty et al. 2009). Conversely, following social defeat stress in male mice, IKK-mediated NF κ B signaling promotes social avoidance behavior (Christoffel, Golden et al. 2012) and led to an increase in the number of stubby dendritic spines on medium spiny neurons in the NAc (Christoffel, Golden et al. 2011). In these studies, activation of IKK signaling pathway was found to be necessary and sufficient to mediate both behavioral and structural alterations. Environmental stressors, including exposure to several drugs of abuse such as cocaine (Ang, Chen et al. 2001, Russo, Wilkinson et al. 2009) and alcohol, also upregulate NF κ B signaling in the nucleus accumbens.

NF κ B-mediated alterations in synaptic plasticity also appears to be important for encoding and retaining fear memory particularly in the amygdala. A single two-hour session of cold restraint stress upregulated NF κ B protein expression in the hippocampus, hypothalamus, amygdala, NAc, and PFC, and the antidepressant citalopram partially restored NF κ B levels in the hippocampus and amygdala (Garabadu, Reddy et al. 2015). An increase in NF κ B DNA-binding was found to be required in the rat amygdala during fear potentiated startle as well as LTP induction that are necessary for fear memory consolidation (Yeh, Lin et al. 2002). Furthermore, fear conditioning was found to increase acetylation of the p65 subunit of NF κ B, and promote long-term retention of fear memory (Yeh, Lin et al. 2004). Collectively, the available data to date demonstrate a plausible role for both GR and NF κ B in modulation at the synaptic level, but this does not rule out additional mechanisms by which both transcription factors may modulate neural function and thereby behavior.

6. Influence of Age and Sex on GR-NF κ B Interactions

In order to promote clarity, the discussion to this point has focused primarily on adult endpoints and has not attended to sex differences. However, both development and sex

differences are key variables to consider in attempts to characterize and understand GR and NF κ B.

6.1 Development

Chronic stress paradigms alter inflammatory responsivity differently throughout development. Males and females undergoing prenatal stress exhibit an exaggerated corticosterone response following IL-1 β challenge or exposure to acute restraint, and only females exhibit decreased GR mRNA in the CA2 region of the hippocampus (Brunton and Russell 2010). In addition, rats that were maternally separated during development exhibit a prolonged HPA response following acute stress exposure and decreased GR mRNA in the hippocampus (Ladd, Huot et al. 2004). In reference to immune challenge as the primary signal, early life exposure to an immune challenge may alter the balance between glucocorticoid and inflammatory signaling through adulthood. Rats exposed to a neonatal LPS challenge exhibit a decreased febrile response when subsequently challenged with LPS in adulthood, coupled with reduced expression of pro-inflammatory cytokines and reduced phosphorylation of I κ B α . In addition, following neonatal immune challenge, rats also exhibit an increased corticosterone response to LPS, and impairing glucocorticoid signaling via adrenalectomy or treatment with the GR inhibitor RU-486, restored normal febrile and cytokine response to LPS challenge (Ellis, Mouihate et al. 2005). These data highlight the importance of inflammatory exposure during development in long-term alterations in the balance between GR and NF κ B signaling, effects that occur throughout the lifespan. Furthermore, the impact of stress exposure and immune challenge on behavior and glucocorticoid regulation may pass through generations (Grundwald and Brunton 2015).

6.2 Sex Differences

Implications of developmental exposure to stress and inflammation can be influenced by sex. Though much of the mechanistic research concerning mechanisms of GR and NF κ B activity were performed *in vitro*, recent studies have examined sex differences in the interactions of GR and NF κ B activity in the context of stress or inflammatory exposure. For instance, adolescent female rats exposed to chronic stress exhibit impaired nuclear translocation of GR and increased FKBP5 gene expression in the hippocampus following an acute forced-swim stressor (Bourke, Raees et al. 2013), and these effects are coupled with increased depressive-like behaviors in adolescent females (Bourke and Neigh 2011). However, these alterations in GR signaling were absent in adolescent male rats who underwent chronic stress (Bourke, Raees et al. 2013). In addition to impacting GR function and regulation in a sex-specific manner, exposure to chronic adolescent stress may also exert sex-specific influences on inflammatory processes. Males with a history of chronic adolescent stress, while unchanged on baseline metrics, exhibit an exaggerated hippocampal pro-inflammatory response including enhanced expression of TNF- α , IL-1 β , and I κ B when challenged with LPS in adulthood (Pyter, Kelly et al. 2013). This inflammatory priming effect was not seen in female rats that underwent chronic adolescent stress. Chronic immune activation may also lead to sex-specific alterations in GR-NF κ B dynamics. Treatment of rats with LPS for seven days led to increased nuclear accumulation of NF κ B and depressive-like behavior in both male and female rats. However, while females displayed elevated nuclear GR, males displayed increased cytosolic GR, suggesting a potentially male-specific effect of

impaired GR inhibition of NF κ B (Adzic, Djordjevic et al. 2015). Although DNA binding or transcriptional activity was not measured in this study, and thus the relative effects of elevated nuclear GR and NF κ B could not be determined (Adzic, Djordjevic et al. 2015), a separate study demonstrated a male-specific effects of LPS on nuclear glucocorticoid receptor expression 24-hours following the final LPS treatment (Brkic, Petrovic et al. 2016).

7. Conclusions

Through this review we have highlighted multiple mechanisms through which GR and NF κ B activity can be modulated and provided examples of alterations in their activity and interactions in neuropsychiatric disease and models of chronic stress and chronic inflammation. Although the specific role of GR and NF κ B in neuropsychiatric illness and the precise implications of altered balance between GR and NF κ B-mediated transcription are unclear, it is evident that the two transcription factors impact activity of each other at multiple levels and treatments aimed at one will likely impact the other.

Understanding of the interactions between these transcription factors may yield therapeutic benefit. It is already known that following cognitive behavioral stress management, upregulated genes exhibit an overrepresentation of GREs and an underrepresentation of κ REs, suggesting that with stress management, patients experience a shift to increased GR-mediated signaling and possibly more adaptive function (Antoni, Lutgendorf et al. 2012). Additional therapeutic avenues may be feasible through modulation of the molecular mechanisms that mediate these transcription factors such as interventions at the level of FKBP5 (Hinds, Stechschulte et al. 2014, Gaali, Kirschner et al. 2015, Hartmann, Wagner et al. 2015, Maiaru, Tochiki et al. 2016) which interacts with both GR and NF κ B (Rein 2016). Furthermore, several anti-inflammatory and anti-cytokine agents have been considered for the treatment of mood disorders with moderate success. Some of the more successful anti-inflammatory strategies are NSAIDs and target the COX-2 pathway which is downstream of NF κ B (Bremner and Heinrich 2002). Given the extensive crosstalk between NF κ B and GR, amelioration of NF κ B dysfunction is likely to reciprocally facilitate improved function of GR. Through continued study of GR and NF κ B with attention to the nuances of the effects of these transcription factors and targeted strategies to modify their intricate interactions, improved intervention strategies for stress-induced and inflammatory disorders of both the central nervous system and other functions subject to the balance between the endocrine and immune systems may be achievable.

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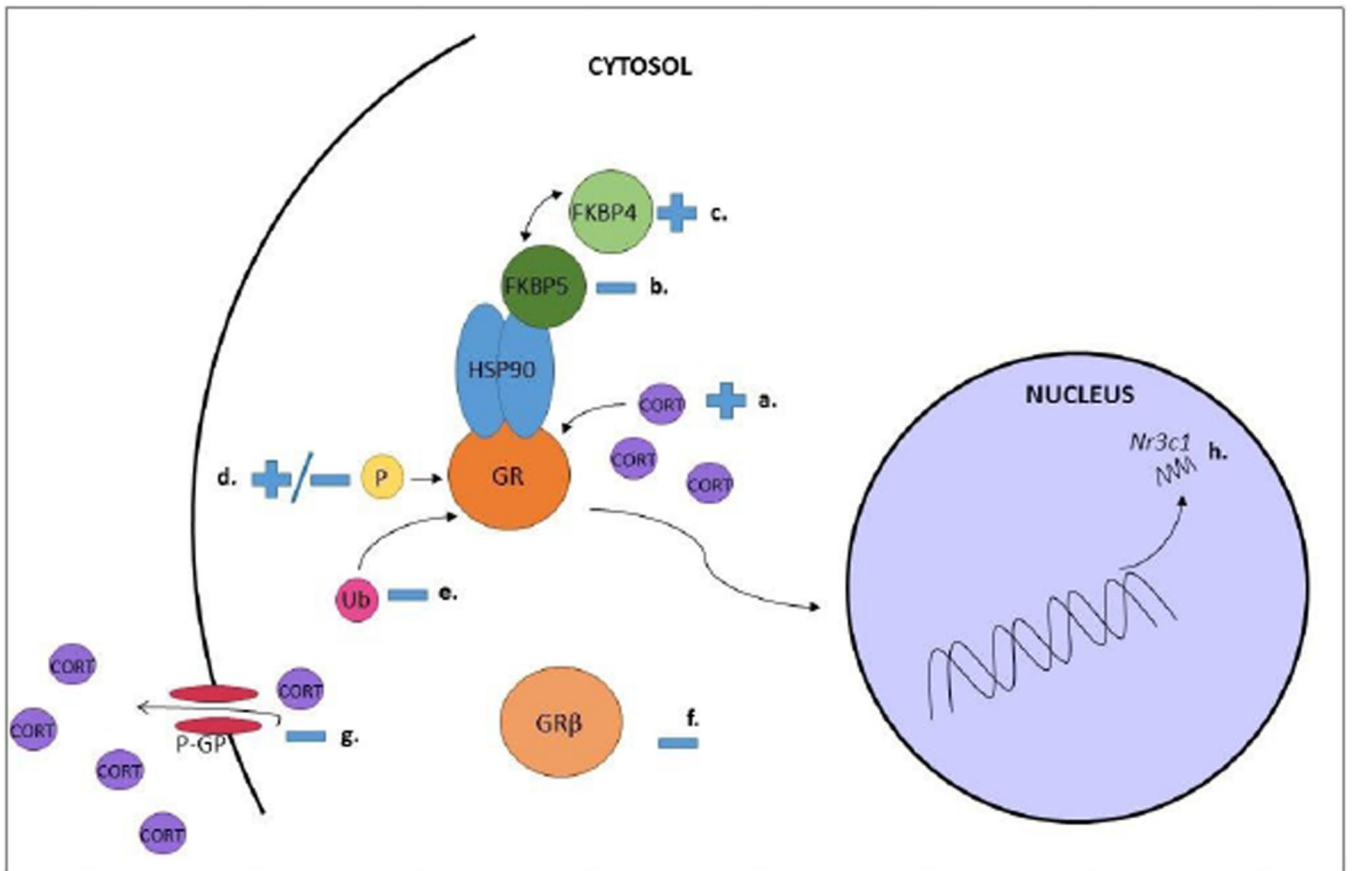
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Highlights

- The endocrine-immune balance is disturbed by environmental or psychosocial stressors.
- Concurrent GR and NF κ B dysregulation is seen in stress-linked psychiatric disorders.
- Mechanisms of GR-NF κ B interactions are discussed in states of health and disease.
- Chronic stress shifts GR-NF κ B dynamics in brain regions underlying mood and behavior.
- Developmental influences and sex differences modify the GR-NF κ B balance.



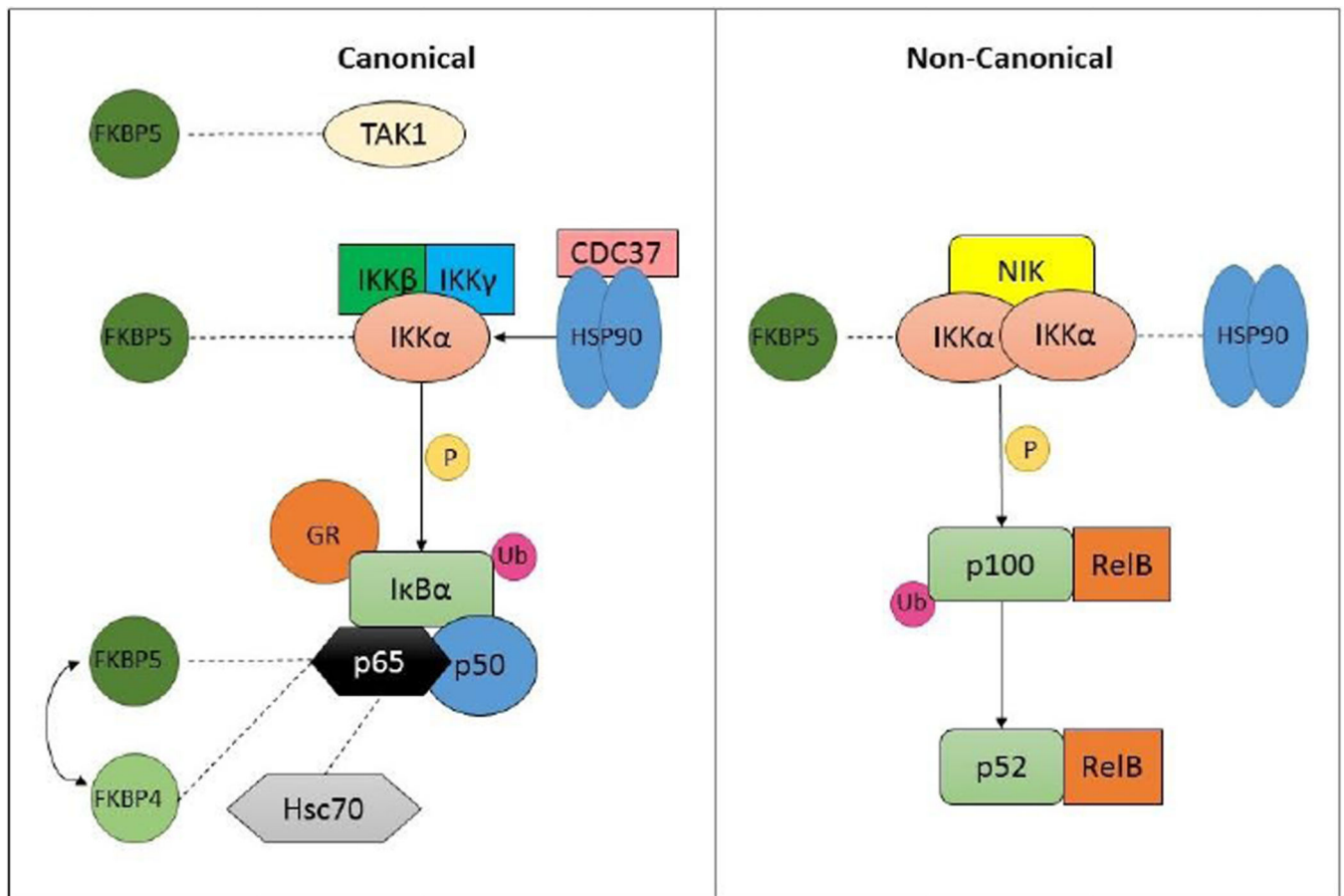


Figure 1.

A. Molecular Regulation of GR Activity of the GR is regulated at multiple levels. Glucocorticoids (CORT), the ligand for the GR, promote nuclear translocation activity of the GR (a.). Co-chaperones of the GR such as FKBP5 (b.) and FKBP4 (c.) impair or promote GR nuclear translocation respectively. The GR is phosphorylated (d.) at multiple sites which may increase or decrease GR activity, and furthermore, the phosphorylation status of GR may alter the transcriptional profile, providing fine-tuning of the genes GR up or down-regulates. Ubiquitination (e.) promotes degradation of the GR, reducing GR activity. Expression of GR β (f.) may decrease activity of the GR, and increased efflux of the ligand CORT from the cell due to increased p-glycoprotein activity (g.) may also decrease activity of GR. Altered transcription of *Nr3c1* (h.) may also impact GR expression and activity.

B. Molecular Regulation of NF κ B. The canonical and non-canonical NF κ B pathways reside in the cytoplasm, tethered by the inhibitor protein I κ B α /p100/p105. Following TAK1-mediated activation by TNF, IL-1, and Toll-like receptor transduction pathways, the canonical IKK complex phosphorylates I κ B α , thus releasing the p65-p50 heterodimer to translocate to the nucleus. In the non-canonical pathway, following activation by lymphotoxin- β receptor or CD40 ligand signaling, IKK α phosphorylates p100/p105, thus triggering their cleavage into p52/p50. The newly freed p52/p50-RelB complex then translocates into the nucleus. The NF κ B complex may be subject to further post-

translational modifications including phosphorylation and acetylation prior to binding to the κ REs.

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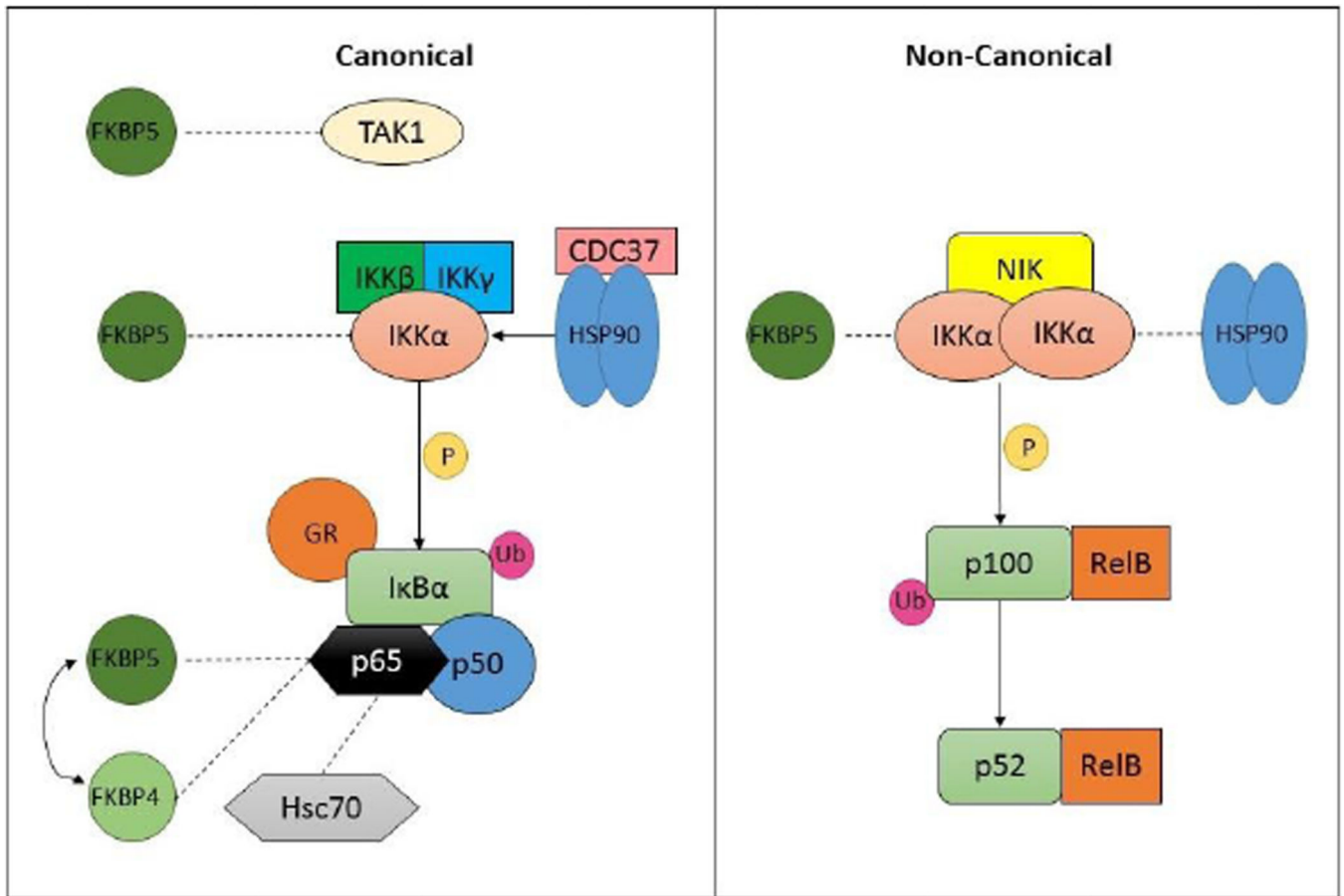


Figure 2. Cytoplasmic interactions between GR and NFκB cascades

The co-chaperone FKBP5 has been identified as a binding partner to multiple proteins constituting the NFκB pathway including TAK1, IKKα, and p65. Furthermore, the chaperone proteins CDC37, Hsp90, and Hsc70 also bind IKKα and p65. The functional significance of these protein-protein interactions remain incompletely understood.

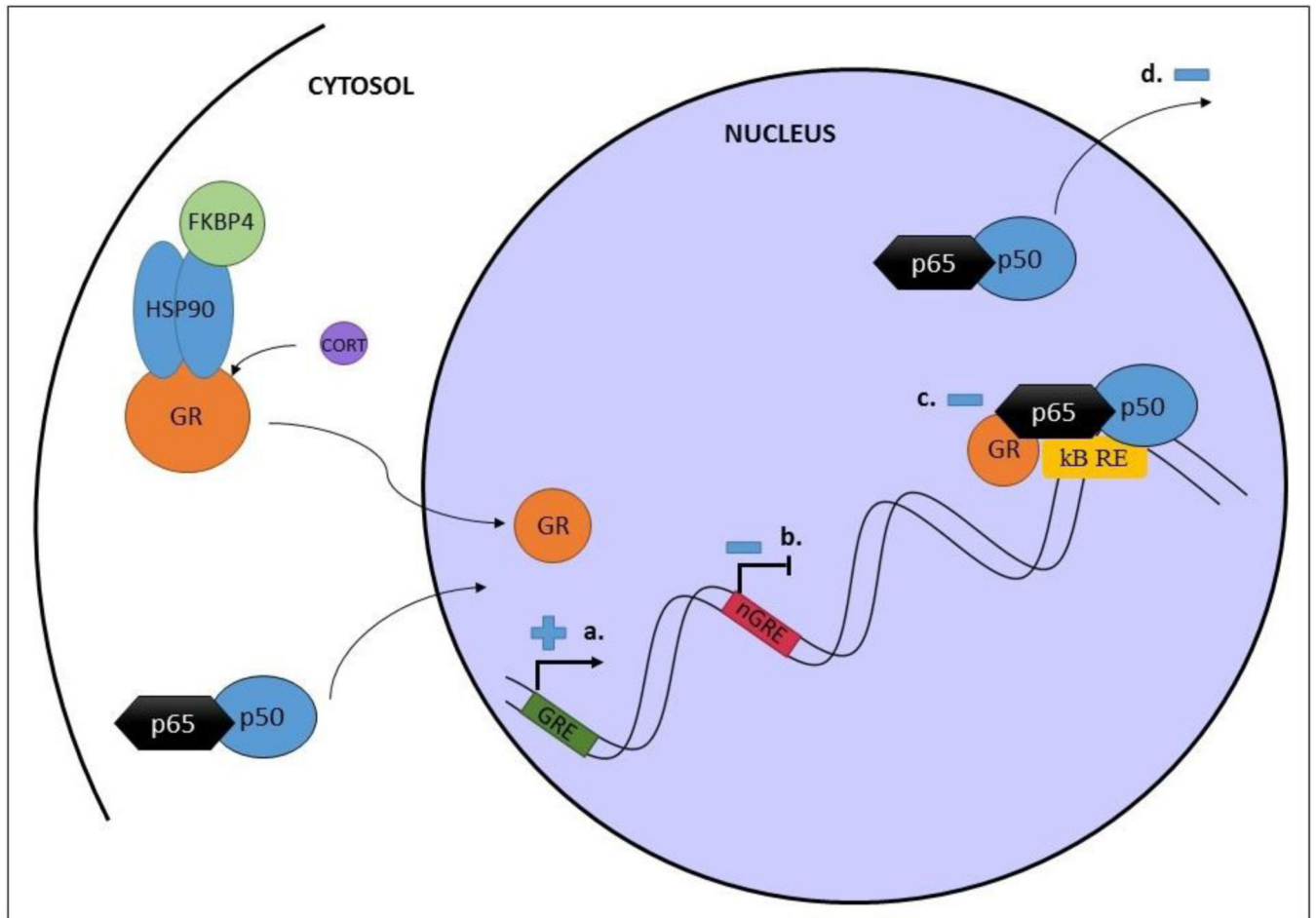


Figure 3. Nuclear interactions between GR and NFκB cascades

The GR interacts with GREs (a.) and negative GREs (b.) to promote or suppress gene expression at numerous target genes. Interactions with these regulatory elements can be reduced by interactions between GR and NFκB. Interaction of GR with the p65 subunit of NFκB (c.) can also inhibit NFκB transcriptional activity at κBREs. Finally, some reports suggest that GR can promote nuclear export of NFκB, further reducing its transcriptional activity.

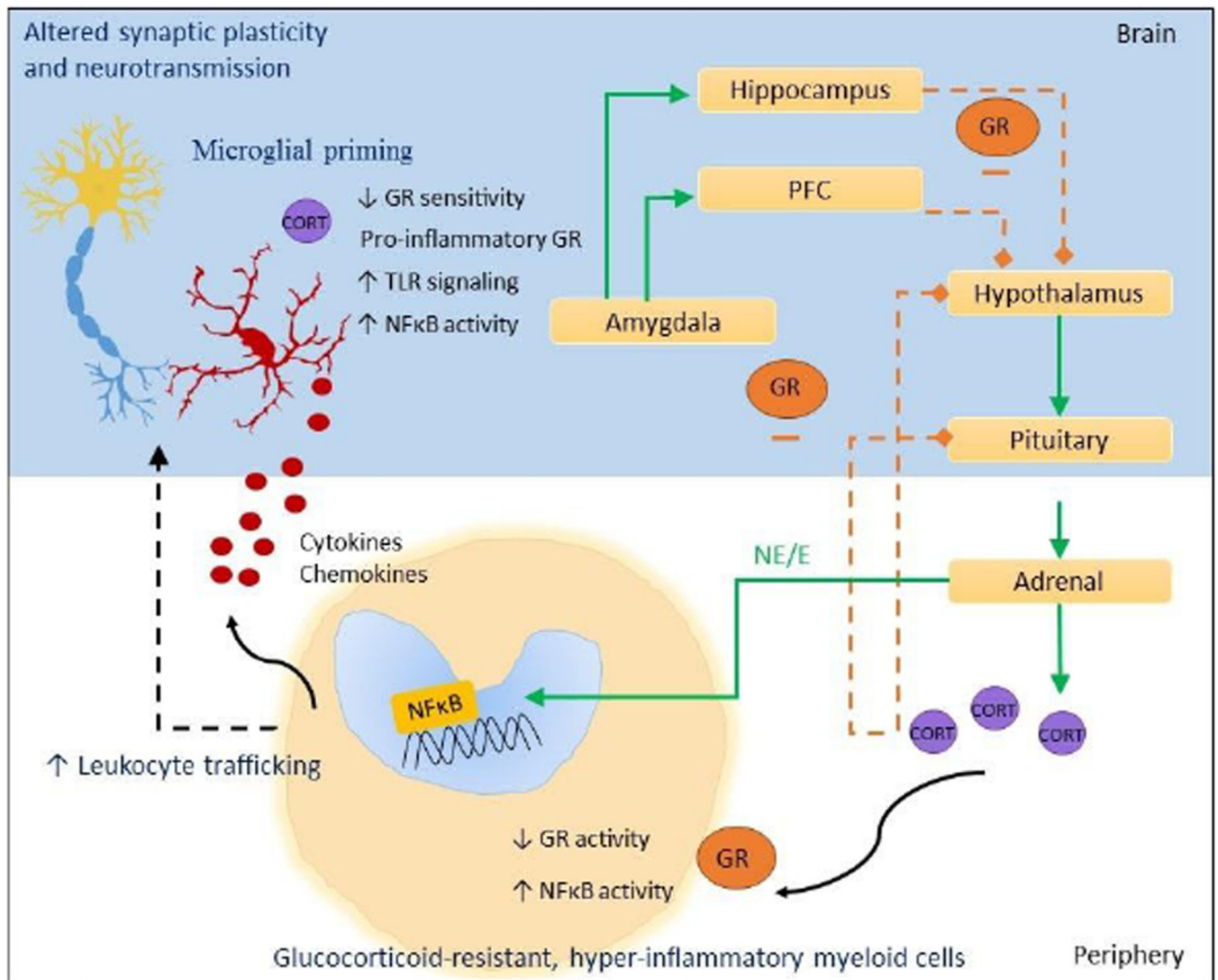


Figure 4. GR and NF κ B in glucocorticoid resistance in the brain and immune system

Under acute stress conditions, release of catecholamines by the sympathetic nervous system activates NF κ B within peripheral immune cells, and leads to expression of cytokines and chemokines. Activation of the hypothalamic-pituitary adrenal axis results in the release of glucocorticoids, and GR suppresses NF κ B in peripheral immune cells. Under chronic stress conditions, impaired GR activity within peripheral myeloid cells can disinhibit NF κ B-mediated inflammation. In turn, glucocorticoid-resistant, hyper-inflammatory immune cells can traffic into the brain, eventually getting recruited to brain regions regulating the stress response. The GR-mediated negative feedback regulation of HPA axis is also impaired in chronic stress pathology, thus further perpetuating stress-induced neuroinflammation. The disruption in endocrine-immune balance appears to be due partly to primed microglia that display decreased GR sensitivity, pro-inflammatory GR, and exaggerated innate immune activation including increased NF κ B and Toll-like Receptor signaling. The functional

significance of the altered GR-NF κ B balance may be manifested in the brain as altered synaptic plasticity and neurotransmission.

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