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Molecular and Cellular Effects of Traumatic Stress: Implications for PTSD

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Abstract

Purpose of Review—Posttraumatic stress disorder (PTSD) is characterized by hyperarousal and recurrent stressful memories after an emotionally traumatic event. Extensive research has been conducted to identify the neurobiological determinants that underlie the pathophysiology of PTSD. In this review, we examine evidence regarding the molecular and cellular pathophysiology of PTSD focusing on two primary brain regions: the vmPFC and the amygdala.

Recent Findings—This discussion includes a review of the molecular alterations related to PTSD, focusing mainly on changes to glucocorticoid receptor signaling. We also examine postmortem gene expression studies that have been conducted to date and the molecular changes that have been observed in peripheral blood studies of PTSD patients. Causal, mechanistic evidence is difficult to obtain in human studies, so we also review preclinical models of PTSD.

Summary—Integration of peripheral blood and postmortem studies with preclinical models of PTSD has begun to reveal the molecular changes occurring in patients with PTSD. These findings indicate that the pathophysiology of PTSD includes disruption of glucocorticoid signaling and inflammatory systems and occurs at the level of altered gene expression. We will assess the impact of these findings on the future of PTSD molecular research.

Keywords

PTSD; Transcriptomics; Genomics; Glucocorticoid signaling; Prefrontal cortex; Animal models of PTSD

Introduction

Activation of the stress system is an important component of an organism's ability to survive challenges to physical safety and maintenance of internal homeostasis and includes activation of endocrine, immune, metabolic, and behavioral systems [1–3]. The cellular

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Compliance with Ethical Standards

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stress response is conserved across all organisms [4], and the molecular consequences of stress, if pathologically induced, can lead to long-term disability in the form of chronic disorders, including anxiety, major depression, and posttraumatic stress disorder (PTSD). Stressful conditions or physical forms of abuse early in life can adversely affect resilience to stressful or traumatic events later in life [5]. Similarly, witnessing or experiencing a traumatic event can lead to long-term consequences to the mental health of an individual. It is likely that changes in the cellular and molecular response to traumatic stress cause long-term effects responsible for the onset of disease.

PTSD occurs in a subset of individuals who have experienced a traumatic stressful event in life. The risk of developing PTSD after a traumatic event ranges from 5 to 31% with the commonly accepted rate being 15% [6–8]. However, in military populations deployed to combat areas, the risk is at the higher end of the range (30%). The reasons why some people develop PTSD while others exposed to comparable trauma do not is not well understood, but likely involves changes in the molecular and cellular mechanisms that govern stress resiliency and susceptibility. These changes could be caused by a preexisting traumatic episode, the severity of the experienced trauma, or genetic heterogeneity in the population [5, 8, 9]. PTSD poses a considerable public health concern because of the debilitating nature of the symptoms and because of the high rates of comorbidity with other psychiatric disorders such as major depression and bipolar disorder [10]. People with PTSD also experience chronic inflammation [11••], metabolic disorder [12], increased incidence of coronary artery disease [13, 14], and increased rates of early mortality [8, 15].

Recent studies that will be discussed report the possibility of several different molecular and cellular signaling pathways in the susceptibility and onset of PTSD. It is also possible that a combination of different molecular abnormalities contribute to the long-term effects of early childhood stress or later life traumatic stress on the development of PTSD. Identifying potential gene transcription networks and disease modules involved in the pathophysiology of PTSD will lead to a better understanding of the underlying pathophysiology of this debilitating disorder as well as new and more efficacious treatment strategies. This article will discuss the molecular mechanisms that have been identified in blood and postmortem brain tissue and examine the relevant neurobiological changes in animal models of PTSD and chronic stress.

Neurobiology of PTSD

In recent years, considerable attention has been focused on studies to elucidate the neurobiology of PTSD with the hope of developing more effective treatments. There is growing evidence that traumatic experiences change neuronal morphology, function and neurochemistry [16], and the ability of the brain to adapt and respond to future stressors [17]. The hypothalamic-pituitary-adrenal (HPA) axis, the major stress responsive endocrine system, also undergoes significant alterations in response to trauma [5, 18, 19]. The HPA axis plays a major role in maintaining homeostasis in the body, including the brain where it modulates levels of certain neurotransmitters and hormones, as well as cellular signaling systems [20]. During fearful situations, the pituitary signals for cortisol to be released by the adrenal glands via release of the pituitary peptide adrenocorticotrophic hormone (ACTH).

Cortisol circulates in the body to exert significant metabolic effects and plays a key role in the reconsolidation and retrieval of fearful memories [7]. The actions of cortisol on cell function are mediated by glucocorticoid receptors (GR) that translocate to the nucleus and regulate gene transcription.

Multiple studies have demonstrated elevated levels of another component of the HPA axis, corticotropin-releasing hormone (CRH), a hypothalamic peptide that signals to the pituitary to release ACTH. These studies report increased CRH in the cerebrospinal fluid of PTSD patients that is directly associated with disease severity, suicide, and psychosis [21, 22]. CRH is expressed in other brain regions and plays a role in stress and fearful responses; activation of CRH signaling or forebrain CRH overexpression in rodents increases startle reactivity (a hallmark of PTSD) and produces sustained anxiety-like defensive behavior [23, 24]. Conversely, CRH receptor antagonism inhibits startle activity [24]. CRH signaling involves the coupling of the CRH receptors, R1 and R2 to a Gαs (G protein, alpha subunit), which activates cyclic AMP-protein kinase A (PKA) signaling; PKA then regulates multiple cellular systems via phosphorylation of cytosolic and nuclear target proteins [25]. Interestingly, pharmacological studies show that antagonism of PKA activity blocks CRH-induced startle hyperreactivity [8], further demonstrating that CRH signaling contributes to hypersensitive PTSD symptoms.

CRH-mediated PTSD-related behaviors, including anxiety and fear, are also dependent on the brain region being examined. For example, CRH activation of another cellular protein kinase, Akt in the ventral tegmentum area (VTA), promotes resistance to anxiety- and depressive-like responses to stress [26] whereas Akt stimulation in the dorsal hippocampus or basolateral amygdala increase fear responses [26]. These brain regions control fundamentally different behaviors (e.g., VTA regulates motivation and reward; amygdala controls fear learning and anxiety), and further understanding of the signaling pathways and interactions of these brain circuits would provide additional insights into the role of CRH in mediating PTSD symptoms. Interestingly, transgenic mice expressing high levels of CRF also develop increased expression of a chaperone protein, FKBP5, that binds to and inactivates GR function; genetic studies demonstrate association of FKBP5 single nucleotide polymorphisms (SNPs) with PTSD [27, 28], suggesting that there is cross talk between CRH and GR signaling pathways that may play an important role in PTSD pathophysiology.

Basal levels of cortisol are reported to be low in the blood of PTSD patients (Fig. 1) [29, 30], although there is also conflicting evidence. A meta-analysis of 37 studies reported that blood cortisol levels were not significantly different in PTSD patients compared to controls [31]. However, this study points out differences in collection and analysis as possible caveats; these include number of females in each cohort, time of day during which blood collection occurred, and the nature of the trauma. Cortisol levels are regulated by glucocorticoid-GR feedback signaling at multiple levels of the HPA axis, the hippocampus, and other brain regions and disruption of one or more of these is thought to be involved with PTSD pathophysiology. However, while cortisol levels are featured prominently in the literature, it is important to point out that there is currently no association between GR polymorphisms and PTSD [32].

Traumatic experiences activate several brain regions that have been implicated in the pathophysiology of PTSD, including the prefrontal cortex (PFC) [33–36], amygdala [37–40], hippocampus [36, 41, 42], and the anterior cingulate [43]. White matter connections between the ventral region of the medial PFC (vmPFC) and the amygdala mediate bidirectional communication that regulates fear learning and extinction [44]. The amygdala is a subcortical limbic structure that also communicates with the brain stem and hypothalamus, as well as the hippocampus to regulate components of fear and emotional responses.

Numerous studies have demonstrated that the vmPFC provides important inhibitory control over amygdala function, and the disruption of vmPFC-amygdala communication is thought to play a critical role in the pathogenesis and expression of PTSD symptoms [45]. The amygdala is a key region involved in emotional learning, particularly in the acquisition and expression of fear and anxiety in response to traumatic or stressful events [46, 47]. In healthy individuals, amygdala activity is dampened by inhibitory signals from the vmPFC, which is thought to reduce stress due to fearful or traumatic experiences [33–36, 48]. In patients with PTSD, vmPFC function is impaired and results in over activation of the amygdala and pathological stress and anxiety responses [49–51]. This model is consistent with neuroimaging studies that demonstrate hypoactivation of the vmPFC and hyperactivation of the amygdala in PTSD patients compared to healthy controls [35, 36, 52].

Insights to the functional impact of vmPFC and amygdala have also come from anecdotal evidence from patients with lesions of these brain regions. There is evidence that damage to the amygdala reduces the chances of developing PTSD—consistent with evidence of pathological hyperactivity of amygdala [45, 53]. Surprisingly, veterans who experience lesions of the vmPFC due to wounds sustained in combat are also resistant to developing PTSD [45, 53, 54]. This finding would seem to suggest that the vmPFC plays a more complicated role in PTSD pathophysiology than simply top-down regulation of the amygdala. It is also possible that these findings are complicated by the size and location of the lesions, which could influence nearby PFC subregions with different functional effects. For example, studies in rodents demonstrate that the vmPFC is required for extinction of fear, but that the region dorsal to vmPFC in rodents, referred to as the prelimbic PFC, receives projections from the amygdala and is required for fear learning [55, 56].

Together, these studies raise an important question regarding the molecular and cellular alterations in the vmPFC and amygdala that contribute to the loss or gain of function, respectively, in PTSD. Preclinical studies in rodents as well as next-generation sequencing of postmortem vmPFC and amygdala from PTSD subjects are being conducted to address this question. These studies are discussed in the next section.

Abnormal Gene Expression in the Pathophysiology of PTSD

Neuronal function is controlled at many levels, including the regulation of gene expression. The first step in gene expression is transcription of DNA into mRNA transcripts. Most of the genetic regulation in humans occurs at the level of the transcriptional control of gene expression, which is regulated at multiple levels, including activation/inhibition of

transcription factors, epigenetic changes (i.e., methylation of DNA, acetylation of histones), and the signaling pathways that regulate the latter. The ultimate goal of gene expression profiling is to identify transcripts expressed by certain tissues or cells and the levels of these transcripts. Most gene expression profiling studies fall into two categories: single and multi-transcript studies. The former traditionally uses in situ hybridization or quantitative real-time PCR to identify changes in one or several transcripts in a given tissue. The latter makes use of microarrays or next-generation sequencing to identify many or all of the transcript changes occurring in a particular tissue.

To obtain meaningful data from gene expression studies, it is important to consider the target tissues to be analyzed. While brain tissue is clearly the optimal choice for understanding the neurobiology of PTSD, it is nearly impossible at the present time to biopsy tissue from living patients (this might become possible in the future). This makes postmortem brains of PTSD patients the most relevant tissue source to identify functional biomarkers for PTSD. There are, however, several caveats that must be monitored during postmortem tissue collection. Changes to pH, temperature, and the length of the agonal state (the time between death and collection of tissue) can all affect transcript levels and are a source of intersubject variation [57]. Perhaps the most relevant issue faced in identifying gene expression changes in PTSD brain is the lack of curated brain banks. To address this issue, the Veterans Administration through the National Center for PTSD has begun building a repository of PTSD brain tissue, the National PTSD Brain Bank (NPBB) [58], that is available for research. The few postmortem studies discussed here were conducted with the NPBB brain tissue.

The first study to examine transcript changes in postmortem PTSD identified an increase p11 (S100A10) in PFC (Brodmann area 46) [59••]. The p11 protein plays a well-established role in regulating mood and has been shown to be downregulated in patients with depression [60] It localizes to the plasma membrane and has a primary role in the cell in binding calcium. Studies also show that rats exposed to inescapable tail shock (an animal model of PTSD) have increased levels of p11 in the PFC. This study also found that the synthetic glucocorticoid dexamethasone upregulated p11 expression through the glucocorticoid response elements (GREs) in the p11 promoter. Glucocorticoid regulation of p11 is particularly interesting given the importance of glucocorticoids in the pathophysiology of PTSD and demonstrates a possible mechanism whereby traumatic stress regulates p11 expression.

In a recent study, we reported on the first whole transcriptome analysis of a small cohort of PTSD subjects in dorsolateral PFC (the lateral part of Brodmann areas 9 and 46) [61••]. Among the changes in gene expression that were found was a significant decrease in transcript levels of *serum/glucocorticoid kinase 1* (*Sgk1*) in PTSD subjects compared to controls. *Sgk1* regulates numerous enzymes and transcription factors involved in inflammation, glucocorticoid signaling, and cell proliferation. Notably, *Sgk1* transcription is regulated by GR signaling (Fig. 1) [62]. We found that viral-mediated knockdown of *Sgk1* in the medial PFC induces helplessness and anhedonic behaviors in rats, supporting a functional role for reduced *Sgk1* expression in PTSD. Knockdown of *Sgk1* also resulted in a reduction in neuronal spine synapse density, demonstrating a change in neuronal

morphology linked to PTSD [61••]. Further, we examined the role of *Sgk1* in classical fear conditioning followed by extinction (an animal model of PTSD). *Sgk1* knockdown in the medial PFC elicited no changes in the formation of fear memory/conditioning or on the rate of extinction. However, animals with knockdown of *Sgk1* demonstrated increased freezing behavior during the first time blocks of the context recall (when the animals were placed in the training context) 6 days after fear conditioning. Downregulation of *Sgk1* may therefore enhance the memory of contextual cues associated with traumatic stress.

In another recent report, we combined human postmortem gene expression profiling with neuroimaging to examine the possible disruption of glutamate cycling disruption in PTSD [63]. Live human photon emission topography (PET) was used to measure the difference in levels of metabotropic glutamate (mGlur5). The results demonstrate increased levels of mGlur5 in PTSD patients, suggesting that glutamate cycling and transmission is disrupted. Previous studies have also identified a role for mGlur5 in regulating fear conditioning [64] as well as the acquisition and expression of fear [65]. It is interesting to note that greater availability of mGlur5 correlates with avoidance symptoms of PTSD. The postmortem gene expression study examined how glutamate related transcripts were altered in postmortem subgenual PFC, a subregion of the vmPFC, of PTSD patients. Although there was no significant difference in levels of mGlur5 transcripts between PTSD and matched controls, there was a significant upregulation of SH3 (Src, Homology-3) and multiple ankyrin repeat domains 1 (*Shank1*). This provides a mechanism to explain increased mGlur5 availability as *Shank1* protein binds to and anchors mGlur5 to the cell surface.

One of the most important molecular findings in PTSD research is that patients exhibit abnormally high GR sensitivity [30]. Central to this finding is the immunophilin *Fkpb5* (FK506 binding protein 5), which has become one of the most studied genes in PTSD research. FKBP5 is a co-chaperone of HSP90 that controls GR signaling, including regulation of GR translocation from the cytoplasm to the nucleus; binding of cortisol to GR results in dissociation of FKBP5 and subsequent GR translocation to the nucleus (see Fig. 1). Gene association studies of PTSD have identified four single nucleotide polymorphism (SNP) risk alleles in the FKBP5 gene. rs9470080, rs360780, rs3800373, and rs9296158 that are predictors of adult PTSD onset [66–68]. These SNPs have been linked to other neuropsychiatric findings, including antidepressant response, stress induced onset of major depression, dissociative symptoms in children exposed to trauma or abuse, and abnormal HPA regulation [7, 67]. All four SNPs interact with childhood abuse to predict PTSD lifetime severity including levels of hyperarousal and alterations in reactivity [69]. Further, decreased *Fkpb5* transcript levels have been observed in peripheral blood and subgenual PFC of patients with PTSD [63].

In addition to glucocorticoid signaling, research efforts have been focused on changes in immune function in PTSD [70]. A synthesis of the current literature reveals disruption of inflammatory signaling in PTSD patients [11, 71]. These studies have primarily examined patients currently diagnosed with PTSD, making it difficult to determine whether these changes in immune function are a cause of PTSD or a result of chronic illness. Several studies have identified a reduction in cytokine and colony-stimulating factors in PTSD peripheral blood [27, 72]. One study found PTSD gender differences, with men, but not

women, showing significantly decreased levels of three transcripts in monocytes isolated from peripheral blood (*Pf4*, *Sdpr*, and *Hist1h2ac*) [73]. *Stat5b*, a transcription factor that regulates both the inflammatory and the glucocorticoid system, is reported to be downregulated in PTSD patients [30, 74]. Interestingly, one study identified downregulation of major histocompatibility complex 2 in patients with PTSD [30] (For a complete list of PTSD RNA biomarkers, see Table 1.).

Animal Models of PTSD

Genetic, molecular, and cellular abnormalities contribute to the pathophysiology of PTSD and present a complex challenge to the development of rodent models to understand the neurobiology of this disorder. Because of the difficulty inherent in reproducing the entire complex of features present in PTSD, researchers have largely turned to models that reproduce core behavioral and physiological aspects of the illness. Additionally, animal models provide insight to the neurobiology underlying PTSD-like behavior that cannot be thoroughly investigated in the clinical setting. Here we provide a description of animal models that are currently being used to further our understanding of the pathophysiology of PTSD.

Symptoms of PTSD develop after exposure to traumatic or stressful experiences, so one approach that the researchers have turned to is exposure to stress to model PTSD in rodents. Rodent models of PTSD generally utilize physical (i.e., stressors with the potential for bodily harm) or psychological (i.e., stressors that put animals in proximity to potential threats) stressors alone or in combination to reproduce features of the disorder. Heterogeneity in stress models arises not only through choice of stressor(s) utilized but also through laboratory specific choices in regard to the duration of stress application and the number of stressor exposures utilized. Though care should be taken in interpretation of results based on choice of stressor(s) used, many of the stress models employed demonstrate the ability to produce symptoms associated with PTSD.

Stressor controllability is demonstrated to play an important role in development of multiple features of PTSD. Initial work in the Seligman lab [78] demonstrated that animals exposed to inescapable foot shocks failed to learn an escape behavior that was readily learned by animals that could terminate the shocks by lever pressing. Exposure to uncontrollable stress has subsequently been shown to produce lasting alterations in PTSD relevant behavior and physiology [79]. For instance, uncontrollable foot shock a week prior to fear conditioning has been demonstrated to increase fear expression while uncontrollable foot shock after fear conditioning enhances fear expression, delays extinction, and supports the recovery of fear expression well after extinction training (e.g., spontaneous recovery) [80••]. Additionally, uncontrollable foot shock reduces the response of the HPA axis to subsequent foot shock [81]. These results are consistent with dysregulated fear and HPA axis reactivity in PTSD. A wealth of studies indicate that the PFC is critical for detection of stressor controllability [80••, 82–85] consistent with observations that impaired PFC function may be an important mediator of PTSD symptoms.

Another model is single prolonged stress (SPS), which reproduces multiple aspects of PTSD symptomatology. In a typical SPS experiment, restraint stress is followed by a forced swim exposure that produces unconsciousness [86]. In the SPS model, the back-to-back exposure to physical stressors is followed by a 7 to 14-day period undisturbed in the colony room that is utilized to incubate development of PTSD-like symptoms. This time-dependent incubation of symptoms was previously suggested to be important for development of PTSD, which may arise well after a traumatic event [87]. SPS produces many of the symptoms commonly associated with PTSD. For instance, SPS exposed rats demonstrate enhanced glucocorticoid negative feedback [86], which is thought to underlie the observed decrease in peripheral cortisol levels in PTSD patients [88–90]. Importantly, this is in opposition to reduced glucocorticoid negative feedback typically observed in depressed patients, as well as after multi-week chronic variable stress paradigms used to model depression in rodents [91]. SPS exposed rats also demonstrate increased startle reactivity [92], a measure of anxiety and increased arousal, and increased depression like behavior in the forced swim test [93]. SPS has also demonstrated validity as a PTSD model by producing abnormal fear conditioning [94] and fear responses that are resistant to extinction [95]. Recently, a similar model has been validated in mice across many of the PTSD-associated measures described previously [96].

A hallmark of PTSD is the inability to forget or extinguish traumatic events, and one model that has been used to study this deficit is extinction of conditioned fear in rodents [36, 97]. Rodents are readily conditioned to freeze in an environment in which they have been exposed to a noxious stimulus, such as a footshock. Repeated reexposure to the audio and visual cues but without the footshock results in extinction of the conditioned fear and has been used to study the neurobiology underlying deficits in fear extinction. This model has also been used to test treatments for PTSD that could enhance extinction. Importantly, the vmPFC, particularly the infralimbic PFC in rodents, as discussed previously, is required for fear extinction. We have reported that the rapid antidepressant ketamine enhances the extinction of fear in rats [98] consistent with recent clinical findings that ketamine improves PTSD symptoms in patients [99, 100]. We also found that increased fear extinction was associated with enhanced mTORC1 (mechanistic target of rapamycin complex 1) signaling in the vmPFC and that pretreatment with an inhibitor of mTORC1 blocked ketamine enhancement of extinction. mTORC1 directs cellular translation by signaling through 4E-EBP1 (eukaryotic translation initiation factor 4E binding) and ribosomal S6 kinase [101]. This provides an example of the types of studies that can be conducted to test novel therapeutic agents and characterize neurobiological mechanisms of treatment response and pathophysiology.

While physical stressors clearly also contain psychologically stressful components, stressors that do not pose a direct risk for bodily harm may also be useful for studying PTSD. Predator odor stress models are commonly used to study development of emotional and traumatic behaviors in animals. These studies commonly show that exposure to cat odor is capable of producing prolonged anxiety-like behavior in tests such as the elevated plus maze and is able to act as an unconditioned stimulus to alter behavior when associated with contextual cues [102]. Predator odor exposure has also been shown to impact females to a greater extent than males, consistent with sex differences in the PTSD development in

humans [103]. Additionally, when using Lewis rats, exposure to predator odor has been shown to reflect the individual differences in development of PTSD present in human populations exposed to trauma. Approximately 50% of the Lewis rats develop persistent anxiety like behavior after predator odor exposure, with the remaining 50% of the animals indistinguishable from unexposed animals in the same tests [104]. Notably, the stress sensitive animals demonstrate persistent fear behavior, as well hippocampal dependent memory deficits [105, 106]. It is interesting to note that Lewis rats have a blunted response to stress [104]. This type of effect of stress is observed in patients with PTSD [88, 107] and makes the predator stress models a unique avenue for investigating certain aspects of PTSD that are not possible in the SPSM model.

Another physical stress model, underwater stress exposure [108] also models aspects of PTSD as do social stress models such as social defeat, and models employing housing instability. However, a thorough review of all models is beyond the scope of this review. The models described above demonstrate validity across many behavioral and physiological hallmarks of PTSD and demonstrate the utility of investigating animal models of the disorder.

Conclusions

Currently, our understanding of the molecular components of PTSD is limited. The vast majority of studies looking at the transcript changes in PTSD have been conducted on samples from peripheral blood. Unfortunately, some of these studies have contradictory findings but implicate several biological processes as likely contributors to the pathophysiology of PTSD. Chemokine, cytokine, and interleukin systems are clearly altered in PTSD and are likely to lead to disruption of feedback control of inflammatory processes. Dysregulation of glucocorticoid signaling is a hallmark of PTSD pathophysiology and likely a major contributing factor. There have been numerous studies implicating FKBP5, a GR chaperone protein responsible for nuclear translocation, in both animal models of PTSD, postmortem studies, and in peripheral blood.

Future studies looking at the molecular underpinnings of PTSD will focus on characterizing the abnormal transcriptomic and proteomic changes in PTSD in blood and brain. A recent paper highlighted a need to integrate future postmortem analysis with gene association studies that have already been performed [77••]. This integration of GWAS and transcriptomics is likely to identify the molecular factors most directly responsible for PTSD onset, provide biomarkers for people susceptible to develop PTSD prior to trauma, and identify relevant therapeutic targets. While much has been done to understand the molecular and cellular consequences of PTSD, it is likely that future studies will identify novel pathways, gene networks, and disease transcript modules that underlie the pathophysiology of PTSD onset and expression.

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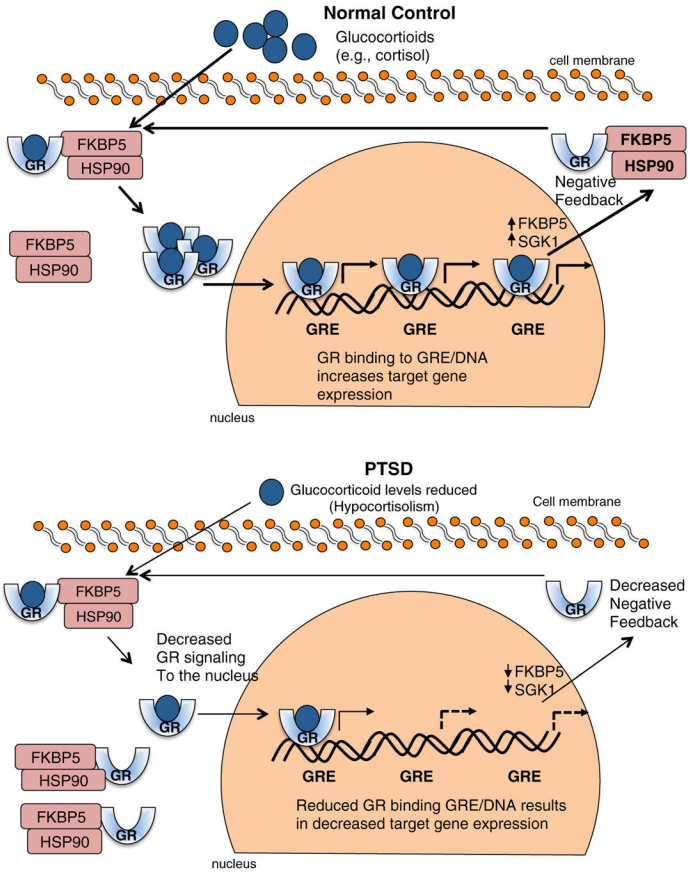

Fig. 1.

Altered glucocorticoid signaling in PTSD. Under normal conditions (top), glucocorticoids (GCs) enter the cell and bind with the glucocorticoid receptor (GR), resulting in dissociation of GR from the chaperone proteins HSP90 and FKBP5. GR is then phosphorylated by a series of kinases (including SGK1) and the GC-GR complex can translocate into the nucleus to regulate gene expression via GR binding to glucocorticoid response elements (GRE). Included in the numerous genes regulated by GC-GR is *Fkpb5*, which provides a mechanism for negative feedback as increased levels of FKBP5 protein can then bind to and inhibit the translocation of GR to the nucleus. PTSD (bottom) is characterized by hypocortisolism or reduced GC levels. This results in less GC available to bind to GR, which then remains associated with FKBP5/HSP90 and blocks nuclear translocation and reduces GC-GR regulated gene expression. This reduction in GC-GR transcription impacts several important genes, including *Fkbp5* and *Sgk1* and disrupts the negative feedback loop necessary to control GR signaling

Table 1

RNA biomarkers of PTSD

Gene	Functional importance	Alteration in PTSD	Study
IL-18	Pro-inflammatory cytokine	Downregulated	Zieker et al. 2007 [72]
IL-16	Pleiotropic cytokine and chemoattractant	Downregulated	Zieker et al. 2007 [72]
CSF-1	Secreted cytokine involved in macrophage development	Downregulated	Zieker et al. 2007 [72]
Igf-2	Cellular growth and mitogenic regulation	Upregulated	Zieker et al. 2007 [72]
P11	Cell cycle progression and differentiation	Upregulated	Zhang et al. 2008 [59]
FKBP5	GC chaperone protein	Downregulated	Yehuda et al. 2009 [30], van Zuiden et al. 2012 [75]
Stat5B	Activated by cytokines and involved in transcription regulation	Downregulated	Yehuda et al. 2009 [30]
MHC-II	Immune response	Downregulated	Yehuda et al. 2009 [30]
PF4	Inflammatory cytokine	Downregulated	Neylan et al. 2011 [73]
Sdpr	Phospholipid binding protein	Downregulated	Neylan et al. 2011 [73]
Hist1h2ac	Linker histone variant	Downregulated	Neylan et al. 2011 [73]
Nfia	Transcription activator	Downregulated	Sarapas et al. 2011 [74]
Sgk1	GC and cell stress response	Downregulated	Licznerski et al. 2015 [61••]
Dicer	Endonuclease involved in miRNA processing	Downregulated	Wingo et al. 2015 [76]
Slc18a2	Monoamine transporter	eQTL SNP associating	Bharadwaj et al. 2016 [77••]
Pzdz8	Cell morphology and cytoskeletal structure	eQTL SNP associating	Bharadwaj et al. 2016 [77••]
Shank1	mGluR5 membrane anchor	Upregulated	Holmes et al. 2017 [75]