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The hypothalamic-pituitary-adrenal axis as a substrate for stress resilience: interactions with the circadian clock

Scott A. Kinlein[1], **Ilia N. Karatsoreos**[1,2,*]

[1]Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA. 99164

[2]Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA 01003

Abstract

Thr hypothalamic-pituitary-adrenal (HPA) axis, engages biological pathways throughout the brain and body which promote adaptation and survival to changing environmental demands. Adaptation to environmental challenges is compromised when these pathways are no longer functioning optimally. The physiological and behavioral mechanisms through which HPA axis function influences stress adaptation and resilience are not fully elucidated. Our understanding of stress biology and disease must take into account the complex interactions between the endocrine system, neural circuits, and behavioral coping strategies. In addition, further consideration must be taken concerning influences of other aspects of physiology, including the circadian clock which is critical for regulation of daily changes in HPA activity. While adding a layer of complexity, it also offers targets for intervention. Understanding the role of HPA function in mediating these diverse biological responses will lead to important insights about how to bolster successful stress adaptation and promote stress resilience.

Keywords

Neurobiology; neuroendocrine; brain; allostasis; circadian rhythms

1. Introduction

1.1 Defining Stress

The term “stress” has a complicated meaning. Stress not only refers to challenges imposed on an organism by the external or internal environment but is also used to describe the processes engaged by an organism to cope with such demands. Stress can be defined as any stimulus or experience which threatens homeostasis [1; 2]. Throughout evolutionary history, these threats were largely imposed by challenges originating in the external environment, such as predation, infection, and starvation. However, while human physiology evolved in these conditions, modern advances in technology greatly reduced the likelihood that one

*Correspondence and Current Address: Ilia N. Karatsoreos, Department of Psychological and Brain Sciences, Center for Neuroendocrine Studies, University of Massachusetts – Amherst, Amherst, MA 01003, T: (413) 545-2383, ikaratsoreos@umass.edu.

would frequently face such direct challenges to survival. In place of these direct threats to well-being, stress in modern society is most commonly experienced in response to internally-generated challenges. Importantly, the same biological systems are engaged whether a person is facing a real threat to survival *or* instead perceives a situation as threatening. The near constant engagement of these systems, in the absence of actual danger from the environment, causes wear and tear on tissues and organ systems throughout the body, increasing susceptibility to disease and accelerating the detrimental processes of aging [3; 4].

The physiological response to stress prepares the body for action in the face of threatening events through the coordinated regulation of biological systems throughout the organism. The biological systems involved in the stress response are highly conserved between vertebrates, and largely rely on the catecholamine and glucocorticoid secretion into the circulation to appropriately synchronize tissue and organ-specific responses to stress [5]. Acutely, these molecules activate classic “fight or flight” processes, by increasing energy availability by stimulating cytokine production, mobilizing glucose in peripheral tissues, increasing cardiovascular tone, while suppressing digestion and reproductive functions [3; 6]. In the face of a threatening situation, these responses increase chances of survival, while reducing investment in processes not directly related to that immediate goal. However, if stress responses are engaged in an exaggerated fashion (e.g. too readily, too frequently), or inadequately, these same processes can cause a breakdown in normal bodily function and predispose an organism to disease (Figure 1) [3; 7].

1.2. Allostasis and allostatic load

The term “allostasis” has been conceived to describe the active physiological process of adapting to stress [8]. While homeostasis maintains individual physiological parameters (e.g. blood pressure, body temperature, blood pH) reactively within a relatively constant range of values necessary for life, allostatic processes are engaged in both an anticipatory *and* reactive manner to maintain homeostatic equilibrium when pressure from the internal or external environment requires one or more of these vital physiological parameters shift outside of their normal range [3; 9]. For example, in anticipation of a threatening situation, and subsequent exposure to a threat, an organism may need to maintain elevated blood pressure and circulating glucose levels in order to escape from a predator or other environmental hazard. The systems that mediate allostasis include the hypothalamic-pituitary adrenal (HPA) axis, the autonomic nervous system, metabolic systems, and the immune system [7]. While helpful in isolated situations of survival, the frequent, prolonged, or inadequate engagement of these systems can lead to wear and tear on tissues and organ systems, an effect defined as “allostatic load”. To continue the example above, while acute increases in blood pressure are helpful in mobilizing a response to an acute threat, chronically elevated blood pressure can lead to hypertension and increased risk for heart failure [3; 7]. The relationship between allostatic load and physiological performance follows an inverted “U” shaped dose-response curve, by which physiological responses to a given challenge that are chronically either inadequate or too excessive can lead to a breakdown in bodily function and the development of disease states (Figure 1) [3; 4].

Understanding the links between dysregulation of allostatic systems and the development of stress-related diseases is one of the key aims of current stress research efforts.

2. The hypothalamic-pituitary-adrenal axis

2.1 Overview

The biological stress response is largely dependent on the release of endocrine signals into the circulation which are produced in response to neuronal transmission at key neuroendocrine junctions. In vertebrates, this coordinated cascade is carried out by the HPA axis. In short, after a stressor is perceived via sensory inputs to the central nervous system, corticotrophin-releasing hormone (CRH) is synthesized and secreted from neurons in the paraventricular nucleus of the hypothalamus (PVH) into the median eminence, reaching proopiomelanocortin (POMC)-containing cells in the anterior lobe of the pituitary via the hypophyseal portal system. This stimulates the synthesis and secretion of adrenocorticotrophic hormone (ACTH) into the circulating blood, which, in-turn, stimulates the synthesis and secretion of glucocorticoids from the adrenal zona fasciculata into the circulation [1; 10]. The primary glucocorticoids secreted by the adrenal gland in response to stress are cortisol in humans and other primates, and corticosterone (CORT) in murine animals. While it has many different biological effects, CORT acts primarily to increase metabolic rate in peripheral tissues by stimulating glucose mobilization [6]. The metabolic effects of CORT work synergistically with the sympathetic nervous system to promote survival in the fight-or-flight response. A key characteristic of the neuroendocrine HPA response is that it functions as a negative feedback loop. Specifically, CORT exerts an inhibitory effect at the hypothalamus and pituitary, which decrease secretion of CRH and ACTH, respectively [11; 12]. This inhibition occurs *directly* via the binding of CORT to glucocorticoid receptors (GR) in these regions, and also *indirectly* via GR binding in upstream limbic brain regions which have inhibitory projections to the PVH and pituitary [10; 13].

2.2 Corticotropin-releasing hormone

CRH is a critical upstream effector of pituitary and adrenal hormone secretion into the circulating blood. This is accomplished through projections from CRH-producing neurosecretory neurons in the hypothalamus to the median eminence, reaching POMC-containing corticotrophin neurons of the anterior pituitary via the hypophyseal portal system [1]. Acting on type 1 CRH receptors (CRHR1) in the anterior pituitary, CRH stimulates the synthesis and secretion of ACTH into the circulating blood. CRHR1 is a G-protein coupled receptor (GPCR) that acts primarily through Gαs coupling [14], and stimulates ACTH synthesis through cAMP-mediated increases in POMC expression [15]. POMC is then synthesized into ACTH through proteolytic cleavage by prohormone convertase enzymes and secreted upon cellular stimulation [16].

In addition to the PVH, CRH is produced in multiple extrahypothalamic regions of the mammalian brain [17], mediating key autonomic and behavioral responses to stress. In support of this, CRH projections from limbic and brainstem structures appear to play a role in locomotor, metabolic, and emotional function during the stress response [18; 19; 20].

Furthermore, selective inactivation of the CRHR1 gene in the forebrain (while pituitary CRHR1 is maintained) results in reduced anxiety-like behavior in response to stress [21].

2.3 Adrenocorticotropic hormone

ACTH is one of many peptide hormones synthesized and secreted by POMC-containing neurons of the anterior pituitary into the circulating blood. This hormone is a critical mediator of glucocorticoid release, acting at the level of the adrenal zona fasciculata to induce the synthesis and secretion of CORT into the bloodstream [16; 22]. The effects of ACTH on glucocorticoid regulation are mediated by type 2 melanocortin receptors (MCR2) in the adrenal cortex [23]. The MCR2 is a GPCR that, when bound to ACTH stimulates adenylyl cyclase and increases intracellular cAMP to promote the synthesis of CORT from 11-deoxycorticosterone by the enzyme 11β-hydroxylase [24; 25]. Importantly, genetic knockout studies have shown that MCR2-deficient mice have undetectable levels of CORT, while retaining normal levels of circulating ACTH [23]. In addition to its roles in glucocorticoid synthesis, ACTH plays a key role in adrenal growth and health. In support of this, ACTH deficiency decreases, and ACTH treatment increases the volume of the adrenal zona fasciculata through effects on cell differentiation [16]. Furthermore, ACTH levels are highly correlated with the expression of antioxidant enzymes, suggesting a protective role of ACTH on adrenal function [26].

2.4 Glucocorticoids

CORT is synthesized and released into the circulating blood by the adrenal cortex (zona fasciculata). This endocrine signal acts on nearly every tissue in the body and nervous system to generally increase energy mobilization, and importantly, also acts as a negative feedback signal to the hypothalamus and pituitary to inhibit HPA output [6; 27]. CORT acts on both mineralocorticoid receptors (MR) and GR, which can modulate both metabolic and neurobehavioral aspects of the stress response [28]. The MR is thought to play an important role in electrolyte homeostasis in the periphery, where aldosterone is the preferred ligand; however CORT is the preferred ligand in the central nervous system [28].The MR binds to CORT with a ten-fold higher affinity than the GR, and thus, even under basal (non-stressed) conditions, it is thought that 80% of MRs are occupied by CORT [29]. Although research into the function of the MR in the brain has been sparse, there is evidence to suggest that these receptors play a regulatory role in the neuroendocrine stress response and also in glutamatergic synaptic transmission [30; 31].

Compared to MR, much more is known about the function of the GR in the brain. The GR is thought to mediate neuroendocrine function under stress-induced levels of CORT, leading to decreases in hypothalamic CRH and pituitary ACTH secretion [32]. This occurs through inhibitory actions of GR in the hypothalamus [33], as well as excitatory effects in key limbic regions of the brain which indirectly inhibit hypothalamic activity, namely the medial prefrontal cortex (mPFC) and hippocampus [34]. The GR exerts its effects through rapid engagement of cellular signaling systems as well as through slower-acting effects on cellular adaptation via control of gene expression [6–8]. The rapid, nongenomic actions of GR in the central nervous system are primarily mediated by membrane-bound receptors [35]. These actions have been well studied in the context of synaptic excitability and glucocorticoid-

mediated negative feedback to the HPA axis (discussed below). For example, in synaptosomes isolated from the mPFC, CORT rapidly potentiates evoked glutamate release through GR-mediated increases in SNARE complex proteins [36]. Membrane-bound GR has also been shown to indirectly influence synaptic excitability through rapid induction of endocannabinoid signaling in the hypothalamus [11]. This implies that nongenomic GR signaling plays an important role in the regulation of excitatory synaptic tone. The genomic effects of GR are mediated by receptors located in the cytoplasm [37]. Once bound to glucocorticoids, a conformational change and phosphorylation by MAP kinase induce translocation of the GR to the nucleus, where GR binds to glucocorticoid response elements (GRE) in the promoter region of target genes [38]. The binding of GR to the GRE then induces gene transactivation or transrepression through the recruitment of general transcription factors [39]. A large portion of the human genome (10–20%) is regulated by the genomic effects of the GR [40]. Included in this group are genes related to metabolism, inflammation, synaptic excitability, and neuronal plasticity [41].

2.5 Glucocorticoid Negative Feedback

2.5.1 Direct feedback to the HPA axis—Direct glucocorticoid-mediated negative feedback to the HPA axis at the level of the hypothalamus occurs through both delayed and rapid feedback mechanisms. Studies have shown that glucocorticoids applied to the hypothalamus decrease CRH mRNA levels, which subsequently reduces the downstream secretion of ACTH and CORT [42; 43]. This delayed glucocorticoid mediated negative feedback in the hypothalamus thus occurs as a consequence of genomic actions of the GR. In addition to genomic action, the presence of glucocorticoids in the hypothalamus quickly reduces glutamate-mediated excitatory synaptic currents in CRH neurons via a GR-mediated mechanism [13]. Rapid glucocorticoid-mediated negative feedback is accomplished primarily by stimulation of local endocannabinoid synthesis and release into glutamatergic synapses; causing an overall depression of excitatory neurotransmission [11; 44; 45]. The contribution of endocannabinoid synthesis to glucocorticoid-mediated negative feedback in the hypothalamus is supported by the following: 1) cannabinoid receptor antagonism completely abolishes glucocorticoid-induced suppression of excitatory post-synaptic currents in the PVH [33; 46], and 2) glucocorticoids increase the levels of the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) in hypothalamic tissue preparations *in vitro* and *in vivo* [46; 47]. Taken together, these findings implicate that both delayed and rapid glucocorticoid-mediated feedback to the hypothalamus are involved in the regulation of HPA output.

2.5.2 Indirect feedback to the HPA axis—Circulating glucocorticoids also negatively modulate HPA output indirectly, via action in limbic brain regions which send projections to the hypothalamus. This indirect feedback occurs via multi-synaptic connections between the mPFC and hippocampus to the PVH, via a sign-changing relay in the bed nucleus of the stria terminalis (BNST) [48; 49]. The involvement of the mPFC and hippocampus in glucocorticoid-mediated negative feedback was initially discovered in lesion studies, which found that damage to either of these regions leads to potentiation of stress-induced glucocorticoid secretion [50; 51; 52]. Additionally, local glucocorticoid administration in these regions reduces HPA output [53].

Anatomical tracing studies have revealed that both the mPFC and hippocampus exert their inhibitory effect on HPA activity via a relay in the BNST [49]. This region has a dense population of inhibitory GABAergic neurons that project to neurosecretory CRH cells in the hypothalamus, down-regulating their activity [49]. Glucocorticoids increase activity of mPFC and hippocampus pyramidal neurons [34; 54], therefore it is hypothesized that circulating CORT works to decrease HPA output indirectly by stimulating excitatory projection neurons in these regions, increasing the activity of inhibitory neurons of the BNST and thus decreasing the activity of neurosecretory CRH neurons in the PVH. HPA axis output can also be indirectly *stimulated* by the central nucleus of the amygdala (CeA). The CeA is thought to stimulate neurosecretory neurons of the PVH indirectly via inhibitory GABAergic projections to the BNST. Consistent with this, lesions of the CeA reduce stress-induced glucocorticoid release and stress-induced anxiety-like behavior [55]. Glucocorticoids may also exert negative feedback actions to the PVH through effects on amygdala function. For example, electrophysiological experiments have revealed that application of glucocorticoids suppresses glutamatergic inputs to the basolateral amygdala (BLA) *in vitro* via effects on non-genomic endocannabinoid signaling [56]. Together, these findings reveal that glucocorticoid-mediated negative feedback to the HPA axis occurs both directly at the level of the PVH and indirectly through the mPFC, hippocampus, and amygdala. Importantly, feedback signals from these brain regions act to modulate HPA output via common connections to the BNST. The multiple mechanisms of glucocorticoid-mediated feedback to the HPA axis highlight the importance of HPA regulation to homeostatic regulation and health. However, these different mechanisms of feedback also highlight the number of possible areas in which dysfunction can emerge to disrupt normal neuroendocrine stress responses and lead to negative health consequences.

3. HPA influences on mood and behavior: Function and dysfunction

3.1 Overview

As discussed above, the effects of stress on physiology and behavior can depend on the frequency and duration of stress exposure. While biological responses to an isolated exposure to stress, referred to as acute stress, generally only have transient effects on metabolic and neural systems, responses to frequent or prolonged exposure to stress, referred to as chronic stress, generally lead to longer lasting changes in the basal functions of these systems. However, we would be remiss if we neglected the fact that a single intense or traumatic stressor can lead to the development of PTSD, which certainly has long-lasting changes in function, and this depends on a variety of risk factors that seem to reduce resilience in humans (detailed meta-analysis; [57]).

The effects of stress on physiology and behavior are highly dependent on the nature of the stressful stimulus experienced. Even though it is likely not possible to completely dichotomize stress into “physical” vs. “psychogenic”, more physical stressors (e.g. blood loss, cold, infection) engage a reflexive systemic response primarily involving the spinal cord and brainstem pathways, while more psychogenic stressors (e.g. restraint, immobilization, novel environment) involve additional processing in forebrain circuits, such as the amygdala, prior to HPA activation [2; 58; 59]. Furthermore, some stressors involve a

combination of physical and psychogenic insults (e.g. foot shock, forced swim). The distinction between stressor types has important implications for interpreting the outcomes of stress exposure, as each may signal via different neural circuits. To directly test this hypothesis, a study by Dayas et. al measured the activation of hypothalamic, brainstem, and amygdala sub-regions following exposure to different stressors [60]. Their findings indicated that while all stressors measured similarly increased the activity of hypothalamic CRH neurons, physical stressors (arterial hemorrhage, ether exposure) preferentially engaged neurons in the rostral region of the dorsomedial medulla and the CeA, and psychogenic stressors (noise, restraint) preferentially engaged neurons in the caudal region of the dorsomedial medulla and the medial amygdala (MeA). Furthermore, Pacak et. al showed that different stressor types have different effects on patterns of brain-wide Fos immunoreactivity and neuroendocrine stress responses [2; 61], further illustrating that the nature of the stressful stimulus can have a large impact on ensuing physiological responses.

In addition to stressor type, the impact of stress on physiology and neural circuits is highly dependent on the chronicity and pattern of exposure. Stress habituation is the process by which the physiological or behavioral responses to stress decrease following repeated exposure to the same (homotypic) stressor over time. However, as discussed by Herman, while stress habituation can reduce the overall physiological burden of chronic stress exposure, it does not represent a return to “normal” physiologic status [62]. Rather, these habituated responses are driven by long-term adaptation in central stress circuits, including the hypothalamus [62]. The central processes of stress habituation appear to be regulated in part by glucocorticoids, as MR antagonism on the final day of repeated exposure to restraint stress prevents habituation of stress-induced CORT secretion [63]. Habituation of the HPA response to stress has been observed in response to repeated exposure to both physical and psychogenic stressors, including restraint, forces swim, and cold stress [64]. However, if an animal is exposed to a stressor that is varied (heterotypic) over time, HPA habituation does not occur to the same extent [62; 65]. Additionally, if an animal is exposed to a novel stressor following chronic stress, they display an exaggerated HPA response [62; 66]. This phenomenon is referred to as stress sensitization, and occurs after both homotypic and heterotypic chronic stress exposure [62]. The process of stress sensitization is thought to be driven in part by chronic stress-induced increases in hypothalamic CRH expression and noradrenergic drive to the PVN which occur as a result of chronic stress exposure [65; 67].

3.2 Modeling HPA dysfunction in rodents

In this section, we will describe four (non-exhaustive) approaches to alter HPA function, as well as the wider brain circuits involved in stress responses, in order to understand how they contribute both to normal, and abnormal, neurobehavioral responses to stress.

3.2.1 Adrenalectomy—The necessity and sufficiency of HPA-secreted hormones to alter physiology and behavior can be tested with various models of removal and replacement. The most widely used method of glucocorticoid removal is bilateral adrenalectomy (ADX). This procedure involves surgical removal or destruction of the adrenal glands, and completely abolishes circulating CORT levels following stress [68; 69]. ADX is useful as it allows one to test the necessity of glucocorticoid secretion to

physiological or behavioral parameters of interest. Additionally, this method allows one to test the sufficiency of CORT in mediating these measures, as known concentrations of CORT can be reintroduced into the circulation via injection or the subcutaneous implantation of a pellet which continuously releases a tonic amount of CORT. ADX has been well-studied for its effects on peripheral metabolism. In both rats and mice, ADX typically decreases body weight gain and white adipose tissue (WAT) deposition [70; 71; 72]. However, some studies in mice report no change in body weight [73], suggesting that the metabolic effects of glucocorticoid depletion may be species-dependent. Furthermore, replacement of CORT via pellet implantation restores normal body weight and WAT in rats, however CORT-induced WAT increases are preferentially deposited in abdominal fat stores [70; 74]. In the brain, ADX increases basal hypothalamic CRH expression and significantly enhances stress-induced ACTH secretion, effects which are not rescued by CORT replacement [53; 69]. Furthermore, while ADX reduces extracellular glutamate responses to stress in the mPFC and hippocampus (discussed above) [75; 76], patterns of c-fos responses to stress across the brain were not affected by ADX or CORT replacement [77].

While the ADX model has been useful for elucidating some important mechanisms of glucocorticoid necessity and sufficiency, the technique has some important limitations in its use as a model of HPA dysfunction for understanding disease states. First, the surgical procedure used to perform ADX may induce pain or stress itself, which leads to confounds when comparing measures between “baseline” and stressed animals. Additionally, the basal increases in hypothalamic CRH and circulating ACTH are confounding in the interpretation of stress-related measures, as these hormones can have direct effects on the processes in the periphery and brain [16; 78]. Finally, while ADX removes plasma CORT responses to stress, other important functions (e.g. aldosterone, epinephrine) secreted by the adrenal are also lost. For example, while ADX completely abolishes circulating epinephrine levels, extra-adrenal epinephrine secretion from the SNS increases as a compensatory response [79; 80], which can cause significant effects on autonomic functions [81].

3.2.2 Genetic models—In addition to directly removing glucocorticoid secretion, disruption of the HPA axis can be achieved using genetic manipulations which interfere with glucocorticoids signaling. Genetic manipulations are useful tools, as they overcome the need for extensive manipulations that may be stressful or harm the animal. Furthermore, many stress-related health disorders have a heritable component [82; 83], giving genetic methods added translational value in understanding the etiology of these diseases. The GR and FK506 binding protein 51 (FKBP5) are main targets for genetic modulation of HPA function, as polymorphisms in these genes are associated with risk of MDD and PTSD [84; 85; 86]. Genetic GR knockout in mice impairs glucocorticoid negative feedback, resulting in elevated levels of circulating ACTH and CORT [87; 88]. Additionally, forebrain-specific GR knockout mice exhibit increased basal CORT levels and show markers of behavioral despair and anhedonia, similar to characteristics of MDD [89]. In contrast, genetic knockout of FKBP5, a negative modulator of GR signaling, results in decreased circulating CORT levels and enhanced GR-mediated negative feedback to the HPA axis [90]. Beyond GR and the HPA-axis, recent work has shown that GABAergic neurons in the forebrain contribute to stress resilience. Genetic deletion of CRH in these neurons can reduce stress-related changes

in neuronal activity, and promotes resilience to stress, suggesting that CRH activity in these neurons may be a critical extra-HPA node the modulates resilience/vulnerability [91].

While these genetic tools are useful in modeling HPA dysregulation, these techniques still possess several drawbacks. First, while polymorphisms in the GR and FKBP5 genes are associated with stress susceptibility, a change in GR or FKBP5 function in humans is different than complete knockout observed in genetic manipulations in mice. For example, global GR knockout is lethal in 90% of mice at the time of birth [88]. Next, in translating the effects of genetic deletion to human health disorders it is difficult to dissociate effects strictly affecting HPA axis function vs those effects caused by interruption of normal developmental processes. For instance, glucocorticoid signaling is involved in processes of neuronal migration and myelination of the developing brain [92; 93]. Furthermore, heritability is estimated to only account for 30–40% of risk for developing either MDD or PTSD [82; 83], indicating that results obtained from genetic knockout studies cannot fully explain mechanisms of stress vulnerability in the human population. While these genetic approaches are important for the physiological dissection of the circuits underlying HPA function and dysfunction, their relevance for many diseases/disorders is likely limited. A more powerful approach may be to more fully characterize the functional changes in other gene mutations outside of classic HPA-axis/stress pathways that are known to modulate resilience and susceptibility to stress-related neuropsychiatric disease. For instance, the val66met polymorphism in brain derived neurotrophic factor (BDNF) is associated with altered stress resilience in humans [94; 95; 96; 97], and work with the as has val66met humanized mouse line aligns well with these findings [98; 99], providing yet another approach to study the effects of extra-HPA factors on stress resilience.

3.2.3 Optogenetic and Chemogenetic models—Contemporary neurobiological approaches that employ genetic tools have allowed for a further dissection of the underlying circuits involved in enhancing resilience or imparting vulnerability. The use of optogenetic and pharmacogenetic approaches has allowed for the temporally restricted manipulation of genetically defined cell-types within different components of the HPA circuitry. Within the HPA, CRH neurons of the PVH contribute to the generation of different stress-induced behaviors, as optogenetic manipulation of these cells can clearly alter their expression and magnitude [100]. Similarly, a local CRH circuit within the PVH has been implicated in both the regulation of the neuroendocrine response to stress, as well as contributing to the activity of PVH targets that are important outputs of this nucleus [101]. Outside of the HPA, similar approaches have provided remarkable new insights into the wider brain networks important in conferring resilience. While the role of the BNST has been well documented in modulation of HPA activity and stress responses via classic neuroanatomical, lesion, and pharmacologic approaches, newer techniques allow for a finer grained dissection of these circuits. Application of optogenetic approaches combined with neuroanatomical tracing has revealed that the anteroventral subdivision of the BNST can inhibit HPA output while also changing passive coping behaviors [102], thus further refining our understanding of the BNST as an important integrative and modulatory node of stress induced changes in physiology and behavior. Use of social defeat models in mice, which causes depressive-like behaviors in a subset of individuals, has uncovered an important role for midbrain

dopaminergic (DA) neurons in resilience. Changes in the biophysical characteristics of ventral tegmental area (VTA) DA neurons following social defeat stress reveals that mice resilient to developing depressive-like behaviors have an enhanced hyperpolarization current, and that by optogenetically increasing this current in susceptible mice imparted resilience [103]. In a similar line of work, locus coeruleus (LC) neurons that project to the VTA have increased firing in resilient mice exposed to social defeat, an effect not observed in susceptible mice. Optogenetic approaches to mimic this increased firing in this circuit can increase resilience in susceptible mice, while pharmacological antagonism of adrenergic signalling in this circuit can block the optogenetic rescue [104]. Related, medium spiny neurons in the nucleus accumbens are implicated in modulating resilience to chronic social defeat, and optogenetic stimulation of these neurons can bidirectionally alter the outcome of this stressor on depressive-like behaviors [105].

3.2.4 Chronic corticosterone via drinking water—Our group and others have shown that chronic treatment with CORT in the drinking water of mice causes changes in HPA activity. For instance, in male mice, the stress-induced rise in CORT is prevented following treatment with oral administration of CORT [106; 107]. Furthermore, in contrast to ADX, which only prevents glucocorticoid secretion, chronic CORT administration also results in reduced hypothalamic CRH mRNA expression and prevents the stress induced rise in ACTH [106]. This reduces confounds of compensatory CRH and ACTH increases observed after ADX. One large advantage of this method is its non-invasive nature as no surgical manipulations or injections are required to achieve downregulation of the HPA stress response, reducing the confounds associated with surgical procedures or injections which may be stressful themselves [108; 109; 110]. An additional benefit is the maintenance of a diurnal CORT rhythm, driven by the diurnal patterns of drinking behavior in mice [106; 111]. The circadian variation in CORT plays a large role in entrainment of central and peripheral clocks, and is known to cause negative effects when absent or flattened [112]. This technique also results in atrophy of the adrenal gland, however reductions are largely localized to the adrenal zona fasciculata (site of glucocorticoid production) while not affecting the adrenal zona glomerulosa (site of aldosterone production) [111; 113]. Thus, the structures supporting other physiological functions of the adrenal gland are maintained while HPA downregulation is achieved, though whether the production or secretion of aldosterone and/or other adrenal factors (e.g. catecholamines) is altered in this model has not been explored. Furthermore, since the adrenal is not removed, this model allows one to investigate recovery, as many of the physiological changes are reversible [113; 114], allowing for the study of long-term consequences of HPA disruption after recovery of normal HPA function. This is a notable advantage in understanding stress-related pathological states, as a history of HPA dysregulation can have long-term effects on health [115; 116]. This method is not without its limitations. For example, this treatment decreases thymus weight, indicating potential impacts on immune function [111; 113]. Also, slight increases in body fat and decreases in lean mass are observed, as well as increases in plasma insulin and leptin, indicating effects on peripheral metabolism [111; 114]. It is also important to note that previous work showed that oral CORT administration at the same dose (25μg/ml) for 20 days resulted in neural structural changes and behavioral despair in mice characteristic of chronic stress exposure [117; 118]. However, these studies used CORT hemisuccinate rather

than un-modified pure crystalline CORT, which resulted in plasma CORT levels after drinking well above physiological levels secreted endogenously during stress (>800ng/ml) [117; 118], while the circulating CORT concentrations achieved by drinking using un-modified CORT are well below stress levels (~100ng/ml) [106; 111].

3.3 Impacts of HPA function on Emotional behavior

Given the pervasive impacts of stress on neural function in limbic brain regions such as the mPFC, hippocampus, and amygdala, it is not surprising that stress also exerts a strong influence on emotional behaviors. Importantly, the expression of these behaviors depends on the internal and external context which they are measured. Behavioral responses to acute stress exposure reflect the engagement of processes necessary for survival, generally including increased vigilance and anxiety and decreased exploration and reward-seeking [3]. In rodents, acute stress exposure increases measures of anxiety, including reduced exploration in the open field test and light/dark transition task [119; 120]. Work by Gray et. al revealed that CRH in the amygdala leads to anxiety-like behavior through an endocannabinoid-mediated mechanism [121]. Specifically, following acute stress, CRH activity in the BLA decreases endocannabinoid levels, disinhibiting the amygdala to then initiate anxiety-like behavior [121]. These results are consistent with other studies which show that genetic knockout of the CRH receptor decreases anxiety-like behaviors in rodents [15]. In the short term, anxiogenic effects of stress may be adaptive in that they increase the chance for an animal to escape acute danger [122]. However, chronic engagement of these behavioral responses can lead to the persistence of anxiety even in the absence of acute threat. For example, Nasca et. al showed that, while anxiety-like behaviors measured in a light/dark transition task were increased immediately after exposure to acute restraint stress exposure in mice, chronic restraint stress caused a similar increase in anxiety even in the absence of an acute challenge [119]. While seemingly negative, these prolonged changes in behavior induced by chronic stress exposure can be thought of as adaptive. As discussed by Herman, increases in anxiety and vigilance minimize risk in a hostile environment, and therefore the development of so-called “pathological” behavior in response to chronic stress exposure may be a way for an organism to overcome present danger at the expense of long-term success [62]. In addition to increasing basal measures of anxiety, chronic stress exposure also increases the expression of “depressive-like” behaviors such as increased behavioral despair and anhedonia, a phenomenon that is of high translational relevance to human stress disorders [123; 124]. In both rats and mice, chronic stress exposure increases measures of behavioral despair (e.g. forced swim and tail suspension test immobility) and anhedonia (e.g. sucrose preference and social interaction) [119; 124; 125]. The mechanisms driving these behavioral changes are not well understood, but can be reversed by treatment with antidepressants [124]. Strong links have been made between dysregulation of glutamate signaling in the mPFC and hippocampus and the development of depressive-like behaviors [126; 127]. While chronic restraint stress increases immobility in the forced swim test and decreases social interaction, these effects can be prevented by pharmacological or genetic overexpression of xCT in the ventral hippocampus [125]. This suggests that changes in synaptic excitability in limbic forebrain structures may underlie the expression of pathological behaviors.

While stress can lead to significant changes in emotional behavior which researchers or clinicians might label as “pathological”, not all individuals exposed to stress will develop these negative outcomes. Understanding the factors which determine an individual’s level of stress resilience or vulnerability is an important task in the goal of treating stress-related psychiatric disorders. Stress coping has emerged as a factor strongly linked to stress resilience. As defined by Koolhaas et al. (1999), this concept refers to the behavioral and physiological efforts made to overcome a stressful situation and depends highly on the perceived controllability of the stressor [128]. Stress coping styles are typically categorized as either proactive or reactive/avoidant in nature [128]. Given that the challenges associated with stress can be complex in nature, relying only one coping style may not necessarily be more successful in every situation. HPA activity is also strongly linked to coping style. Höhne et al. showed that in a sample of subjects with remitted MDD, coping strategy predicted ACTH and CORT responses to an acute stress test [129]. In rodents, proactive and reactive coping strategies are associated with low and high HPA axis stress reactivity, respectively [128]. For example, Pérez-Tejada et al. (2013) showed that mice which exhibited more passive coping behaviors in a repeated social defeat paradigm had greater plasma CORT responses than mice which showed more active coping behaviors [130]. Previous work from our group showed that chronic disruption of normal neuroendocrine HPA stress reactivity in mice is associated with altered stress coping responses in a novel open field test [106; 131]. We showed that following chronic oral administration of glucocorticoids, mice were more resistant to the effects of acute swim stress on self-grooming (reactive) behavior and rearing (proactive) behavior compared to vehicle-treated controls [106; 131]. In addition, these coping responses following acute stress exposure were not dependent on acute glucocorticoid secretion, as acute inhibition of CORT synthesis with metyrapone prior to stress had no effect on open field grooming or rearing behaviors, and acute CORT replacement during stress did not rescue normal stress coping after stress in HPA-disrupted mice [131]. These studies indicated that HPA dysregulation may chronically alter the function of neural circuits underlying stress coping behaviors. We specifically tested how HPA disruption affected the activity of the PVH and the paraventricular thalamic nucleus (PVT) in relation to these altered stress coping responses, as pharmacological and pharmacogenetic stimulation of these regions is known to affect these behaviors [100; 132]. Following chronic HPA disruption, acute stress-induced FOS protein expression was blunted in the PVH and PVT, mirroring effects on grooming and rearing behaviors [131]. These findings revealed a role of these brain regions in mediating the interactions between HPA hormones and stress coping, however more detailed interrogation of these mechanisms needs to be performed before causal relationships can be identified. Further exploration of these stress-responsive diencephalic brain circuits may yield important findings about the regulation of stress coping and could be important targets for therapeutics aimed at reducing the negative impacts of stress on health.

4. HPA dysfunction as a risk factor for disease

4.1 HPA hormones in major depressive disorder and post-traumatic stress disorder

Dysfunction of the HPA axis, particularly in glucocorticoid signaling, is highly associated with stress-related diseases including MDD and PTSD. A large number of depressed

patients have increased basal cortisol levels and exhibit pituitary and adrenal enlargement [133; 134]. This elevated HPA output in MDD is thought to be mediated by reduced glucocorticoid-mediated negative feedback, an idea which stems from findings that oral administration of synthetic glucocorticoids fails to reduce cortisol secretion in patients with MDD, whereas the same treatment results in robust suppression of cortisol in healthy individuals [134; 135]. In contrast, a significant portion of individuals with PTSD have lower basal cortisol levels and enhanced glucocorticoid-mediated negative feedback [136; 137]. In addition, lower cortisol levels following awakening have been found in patients with PTSD compared to healthy individuals [138; 139; 140]. The dichotomy of HPA reactivity in MDD and PTSD highlights the inverted "U" shaped relationship between stress mediators and health, however while different patterns of glucocorticoid dysregulation are found between these disorders, it is still unclear how they contribute to negative emotional and cognitive outcomes.

In both MDD and PTSD, changes in structure and function of limbic forebrain regions have been observed. In MDD, decreases in hippocampal volume have been observed in both functional imaging studies [141], and in overall mass from brains collected postmortem from depressed patients [142]. These effects have been attributed to neuronal atrophy and reductions in hippocampal neurogenesis, which also occurs following chronic stress exposure in rodents [143]. Similar decreases in overall size of the mPFC and changes in neuronal morphology have also been observed in MDD [144], indicating similar mechanisms mediating stress-induced changes in each region. One study by Stockmeier and colleagues (2004) showed that while pyramidal cells are reduced in size in the hippocampus in MDD, the density of glial cells is increased, suggesting a role of inflammation in these processes [142]. Importantly, high levels of glucocorticoids mimic the effects of stress on neuronal atrophy and reduced neurogenesis in rodents [145; 146], suggesting a direct link between HPA dysfunction and neural outcomes of MDD in the hippocampus and mPFC. Similar reductions in volumes of the hippocampus and mPFC have been observed in individuals with PTSD compared to healthy individuals [147; 148]. Interestingly, these changes were also observed in comparison to trauma-exposed individuals who did not develop PTSD, suggesting that morphological changes in the hippocampus and mPFC may be a cause, rather than effect of PTSD development [147].

A leading hypothesis for stress-induced neuronal atrophy in the hippocampus and mPFC in human disorders and following stress in rodents relates to changes in synaptic excitability [126; 149; 150]. Abnormal increases in glutamate levels following stress can overstimulate NMDARs, leading to calcium-mediated excitotoxicity and synaptic depression [149; 151]. Furthermore, stress-induced synaptic depression can be mediated through actions of glucocorticoids. In support of this, Yuen and colleagues (2012) showed that prolonged exposure to glucocorticoids facilitated degradation of NMDAR and AMPAR subunits in the mPFC, and GR antagonism blocked repeated stress-induced decreases in excitatory NMDA and AMPA currents [152]. These results suggest that glucocorticoid-mediated synaptic depression may be a compensatory mechanism to reduce excitotoxicity caused by pathological levels of stress and highlight how HPA dysregulation could contribute to increased vulnerability to negative health outcomes related to stress. In addition to glucocorticoids, dysregulation of CRH signaling may also contribute to negative outcomes

of stress exposure. In support of this, significantly higher cerebrospinal fluid concentrations of CRH have been observed in individuals with MDD or PTSD, and reduced CRH binding sites have been observed in the frontal cortex of suicide victims [153; 154; 155]. Furthermore, pharmacological or virally-mediated increases in CRH in the brain increase measures of anxiety in rodents, suggesting that CRH signaling is mechanistically linked to control of emotional behavior [156; 157]. However, despite these findings, pharmacological treatments targeting CRHR1 signaling have not been particularly effective in the treatment of MDD, suggesting that the role of dysregulated CRH in human psychiatric disorders may involve other CRH receptor types or interactions with other neurotransmitter systems [158].

4.2. Effects of Disrupted HPA function on Resilience: Timing Matters

Most research on stress and HPA function focuses on the major changes observed in HPA activity following acute and/or chronic stress. However, there is a more subtle aspect of dynamic change in the HPA that does not always receive adequate empirical attention: the influence of time of day on HPA activity, and the importance of this circadian influence on optimal neurobehavioral function and adaptive responses. Circadian rhythms are found in nearly all organisms, from single-celled bacteria to humans. A circadian rhythm is a rhythm that persists in the absence of external cues, and thus is endogenously generated. Current models suggest that circadian rhythms allow organisms to anticipate daily changes in the environment, rather than merely respond to such changes. The circadian system is comprised of both central and peripheral clocks, which work in concert to produce coherent behavioral and physiological rhythms in an organism. In mammals, the master circadian clock is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. This was determined by both lesion studies, which unequivocally demonstrated this necessity of the SCN in generating rhythms [159; 160; 161; 162], and transplants of SCN tissue that restored rhythmicity in hosts whose own rhythms have been eliminated by SCN lesions [163; 164; 165]. Though it is undeniable that the SCN is the master circadian clock, the circadian system can be considered as a hierarchical network of control nodes throughout the brain and body. While the SCN is the master clock it controls a network of oscillators throughout the body, which interact with each other. Given that circadian rhythms have been uncovered in nearly every physiological system, from activity of the HPA axis (details below), to food intake and metabolic processes [166], to immune function [167], and neural plasticity [168], this distributed pseudo-hierarchical model of circadian control is well supported. Taken in this context, it is therefore clear why disruption of the circadian clock has widespread, integrative, and in many cases hormetic effects on the organism, thus affecting the ability of many systems to respond to environmental and/or psychological challenge.

Directly addressing the HPA axis, in all vertebrates that have been examined, including humans, non-human primates, and rodents, circadian fluctuations in glucocorticoid secretion that continue in constant conditions have been observed [161; 169; 170; 171; 172; 173]. In fact, the lack of glucocorticoid rhythms following SCN lesions in rats, were among the first data implicating the SCN as a brain clock [161]. In both nocturnal and diurnal animals, the phase of the rhythm differs, with corticoid secretion beginning to rise before waking, though this may be at the start of the day (in diurnal animals) or start of the night (in nocturnal species) [174; 175; 176]. The SCN is necessary for overt circadian rhythms in CORT. As

noted above, lesions of the SCN completely eliminate CORT rhythms [161; 177]. Circadian "forced desynchrony", which disrupts SCN function can also drive changes in CORT rhythms in rats [178]. Though the adrenals possess the necessary molecular machinery to generate circadian rhythms, adrenal rhythms of clock gene expression are SCN dependent [179]. There are two efferent pathways from the SCN that have been implicated in regulation of the HPA. The first is a monosynaptic projection from the SCN to the CRH neurons in the PVN [180; 181]. Output from the PVN is clearly important in both generating CORT rhythms, as well in response to acute stressors. In addition to this monosynaptic pathway, a multisynaptic SCN-Adrenal cortical pathway has also been described [182]. However, the specific role of this pathway has not yet been fully characterized.

In addition to broad rhythms in CORT and HPA axis activity, it is important to explain the origins of these rhythms in CORT. Heroic work by the Lightman group demonstrate that circulating CORT rhythms are generated by alterations in the profile of pulsatile secretion, occurring in an ultradian fashion, with a period of about 1hr [183; 184; 185]. This ultradian pattern of CORT secretion is driven by feed-forward mechanisms and timed delays in processes at both the pituitary and adrenal levels, and unlike pulsatile rhythms in reproductive hormones, it does not require a pulse generator in the hypothalamus [185]. The significance of these ultradian pulses for overall function is an area of high research activity, with additional findings showing that the adrenal responds optimally to a pulsatile pituitary adrenocorticotropic hormone (ACTH) profile, given that constant ACTH infusion results in significantly reduced CORT levels [186].

Circadian rhythms can be found in many aspects of the HPA axis, and in the brain regions that are important for both cognitive and emotional function. Clock genes, the molecular "gears" of the circadian clock are clearly found at every level of the HPA axis. In the adrenal, clock genes seem to underlie rhythmic responsiveness of the adrenal to pituitary ACTH, and to physiological and physical stressors [179; 187; 188; 189; 190; 191]. A large body of work has illustrated that the core clock protein PER2 is rhythmic in extra-SCN brain areas, including the oval nucleus of the BNST (BNST-OV), and the central (CEA) and basolateral nuclei of the amygdala (BLA) [192; 193]. What makes these rhythms noteworthy is that while BNST-OV and CEA rhythms depend on an intact adrenal, BLA rhythms in PER2 are not affected by adrenalectomy. Indeed, CORT is a key player in this rhythm, as PER2 rhythms in BNST and CEA can be restored with CORT in the drinking water (i.e. a somewhat rhythmic route of administration), but not by subcutaneous pellets (i.e. tonic CORT) [194]. In addition to these subcortical regions, a role for diurnal CORT rhythms has been uncovered in cortical areas, being important for spine turnover in motor cortex and driving performance in motor learning tasks [195]. More recent work has demonstrated that CORT can modulate clock gene expression in the PFC of rats, and these effects can modulate fear learning [196].

4.3 Connecting Circadian Rhythms and HPA Function to Resilience/Vulnerability: A model

We and others have suggested that allostatic load, and overload, contribute to increased vulnerability to stressors, and that buttressed allostatic systems could potentially impart

some resilience. But what factors determine how “well” allostatic systems respond to a rapidly changing set of circumstances? Our proposal is that underlying allostasis and the capacity for resilience is an intact and optimally functioning circadian timing system. Our hypothesis is that disruption of the circadian rhythms shifts the organism into a state of higher allostatic load, now being less able to adapt to additional stressors, or changes in stress severity. Evidence exists demonstrating that in rats lacking normal circadian patterns of CORT the HPA axis response is dysregulated, with unreliable/slow termination of the adrenocorticotropic hormone (ACTH) response following the end of a stressor [197]. As noted above, adrenal clock genes also seem to gate normal ACTH sensitivity. Given that CORT is a critical intermediary between the SCN clock and peripheral clocks in many tissues, serving as a humoral synchronizer of these extrahypothalamic clocks further substantiates our proposal that an important relationship exists between disrupted circadian timing and allostatic load. Indeed, a recent review by Rao and Androulakis [198] directly explores the importance of circadian regulation of HPA function in the context of allostatic load.

With respect to the contribution of disrupted clocks to phenotypes that closely mirror instances of high allostatic load, both human and non-human animal studies have been undertaken. Humans who suffer from chronic circadian misalignment show abnormalities in neurobehavioral and physiological function. In a study of flight crews who endure more bouts of jet-lag (short-recovery transmeridian crews) versus crews who fly less transmeridican flights (i.e. more north-south flights; long-recovery crews) show shrunken medial temporal lobes, increased reaction time and poorer performance in visual-spatial cognitive tasks [199]. Physiologically, these populations were also different, in that the short-recovery crews had a significant correlation between salivary cortisol levels and medial temporal cortical volumes, while this correlation was not observed in long-recovery flight crews. The significance of this effect in the temporal lobe with respect to resilience merits some speculation, since in PTSD it has been observed that smaller temporal lobes may impart decreased resilience to negative outcomes of stress [200; 201].

Animal models on circadian desynchronization and stress resilience are still sparse. We have developed a mouse model of chronic circadian desynchronization (CD) in which mice are housed in a 20h light-dark cycle (10hrs light, 10hrs dark; T20) compared to standard 24hr cycles. These mice show metabolic signs of allostatic load, with increased weight, adiposity and leptin levels, as well as an imbalance between insulin and plasma glucose, suggesting a pre-diabetic state. The metabolic changes are accompanied by changes in prefrontal cortex (PFC) cellular morphology, mirroring those observed in chronic stress, with CD animals having shrunken and less complex apical dendritic trees of cells in layer II/III of the medial PFC [202]. The effects are very similar to those observed in 21d of chronic restraint stress in rodents, which results in morphological simplification of prefrontal cortical neurons and impairment in prefrontal mediated behaviors, such as attentional set-shifting or other working memory tasks [203]. Importantly, similar effects are observed in humans [204]. Behaviorally, CD animals show cognitive rigidity in a version of the Morris Water maze, being slower to learn a reversed location of a hidden platform and making more perseverative errors by returning to the original location of the platform [202]. At the same time, CD mice display an “impulsive” like phenotype in the light-dark box, while not

showing any outward behavioral anxiety phenotype [202]. Similar work shows that housing mice in a T7 cycle (7hrs light, 7hrs dark) causes particular changes in mood and emotionality, with a direct projection from intrinsically photosensitive retinal ganglion cells to various thalamic regions being implicated [205].

Our model of circadian-allostatic interaction suggests that desynchronization between the master SCN clock and the external environment drives central and peripheral clocks out of phase with each other, leading to the state of internal desynchrony within neural circuits and other critical physiologic systems, such as the HPA axis. This eventually leads to altered neurobehavioral function. A complimentary aspect of this hypothesis is that shorter episodes of circadian disruption could lead to temporary changes in these systems, thereby rendering them more vulnerable to additional perturbation. Thus, both acute and chronic circadian desynchronization results in a whole-body condition that may allow other stressors to overwhelm already compromised networks. Therefore, circadian desynchronization compromises allostatic responses meant to enable organisms adapt to environmental challenge, by disrupting the stress axis, similar to diathesis-stress (e.g. “two hit”) models (Figure 2). Viewing these findings in light of the proposed model could explain many of the epidemiologic findings of increased risk for development of psychiatric, cardiovascular or other physiological syndromes in shift workers or populations undergoing chronic circadian disruption [206; 207; 208; 209].

Unravelling the mechanisms of this link between circadian rhythms and allostatic load has significant importance for biomedicine, as circadian disruption (e.g. shift work and jet lag) and sleep deprivation are both common in the modern world, and an increasing health concern [210].

5. Summary and Conclusions

The HPA axis is neuroendocrine system which helps organisms adapt to and overcome adverse situations through the secretion of endocrine mediators, including glucocorticoids. This system is subject to extensive physiological regulation and equipped to adjust to differences in stressor type, severity, and chronicity. Dysregulation of HPA axis function is associated with many different metabolic and mental health disorders associated with stress, including MDD and PTSD, highlighting the importance of this system in promoting resilience to adversity. The brain is a major target of stress, and HPA hormones have considerable impacts on neural circuits which regulate cognitive and emotional processing. Furthermore, the ability of HPA hormones to adequately bolster adaptive responses to stress are influenced greatly by circadian rhythms in in all biological processes, which can have profound effects on stress susceptibility.

Our current understanding of the biological factors underlying stress resilience is still relatively nascent, and partially obscured by the vast complexity and individual variability present in physiological, neural, and behavioral pathways. Developing models that consider the interactions between these pathways is necessary in the discovery of novel therapeutic strategies aimed at promoting positive adaptation to stressful life circumstances and decreasing the negative burdens of stress on individuals and on society. Indeed, rodent

models, particularly those using chronic psychosocial stress, significantly affect both behavioral and peripheral responses to subsequent physiological challenge [211; 212]. Establishing a unifying theory of stress resilience that incorporates an appreciation of diversity in both biological function and individual experience will be instrumental in improving health outcomes and disease treatment [213].

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7. References

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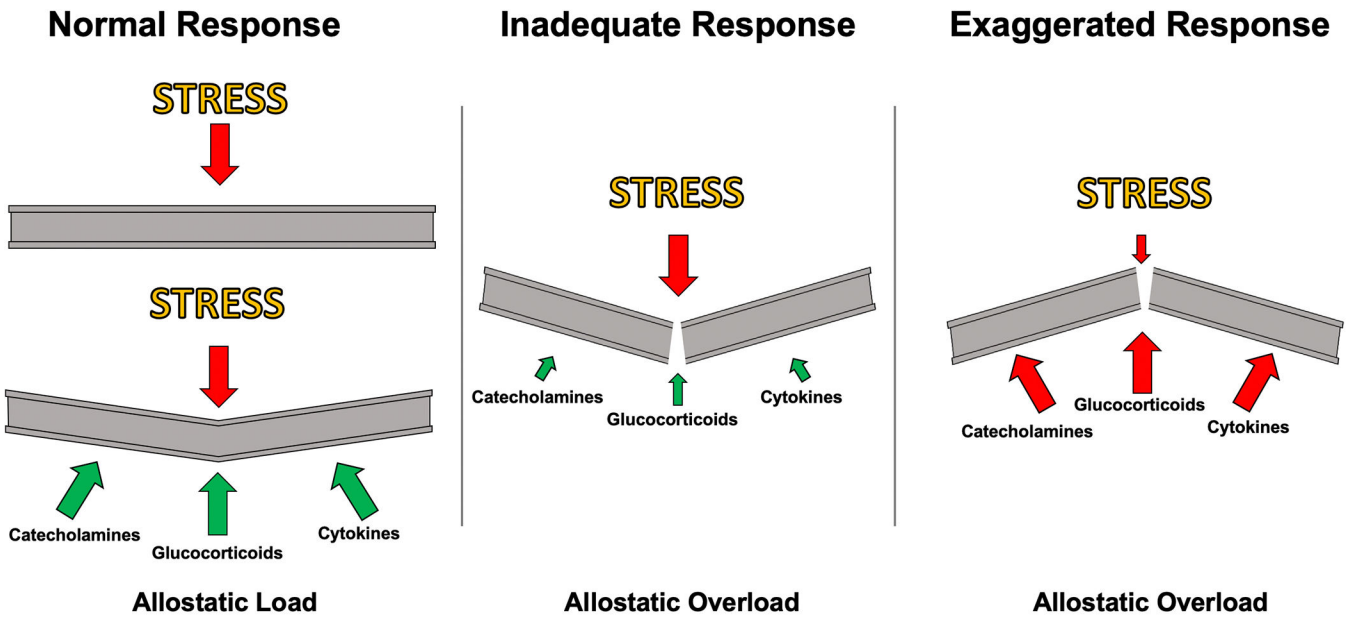

Figure 1. Illustration of interactions between stress and physiological responses can affect stress resilience.

Stress can lead to strain on an organism, and the response (e.g. catecholamines, glucocorticoids, cytokines) supports adaptation to this increased "allostatic load" (left). However, if the stress response is inadequate (middle), or exaggerated/protracted (right), the increased load can lead to the physiological systems being placed into a state of "allostatic overload". In fact, the very stress resposnes that have evolved to enable stress adaptation may lead to allostatic load and overload themselves, even in the face of a small additional stressor (right), which may be a substrate for stress resilience.

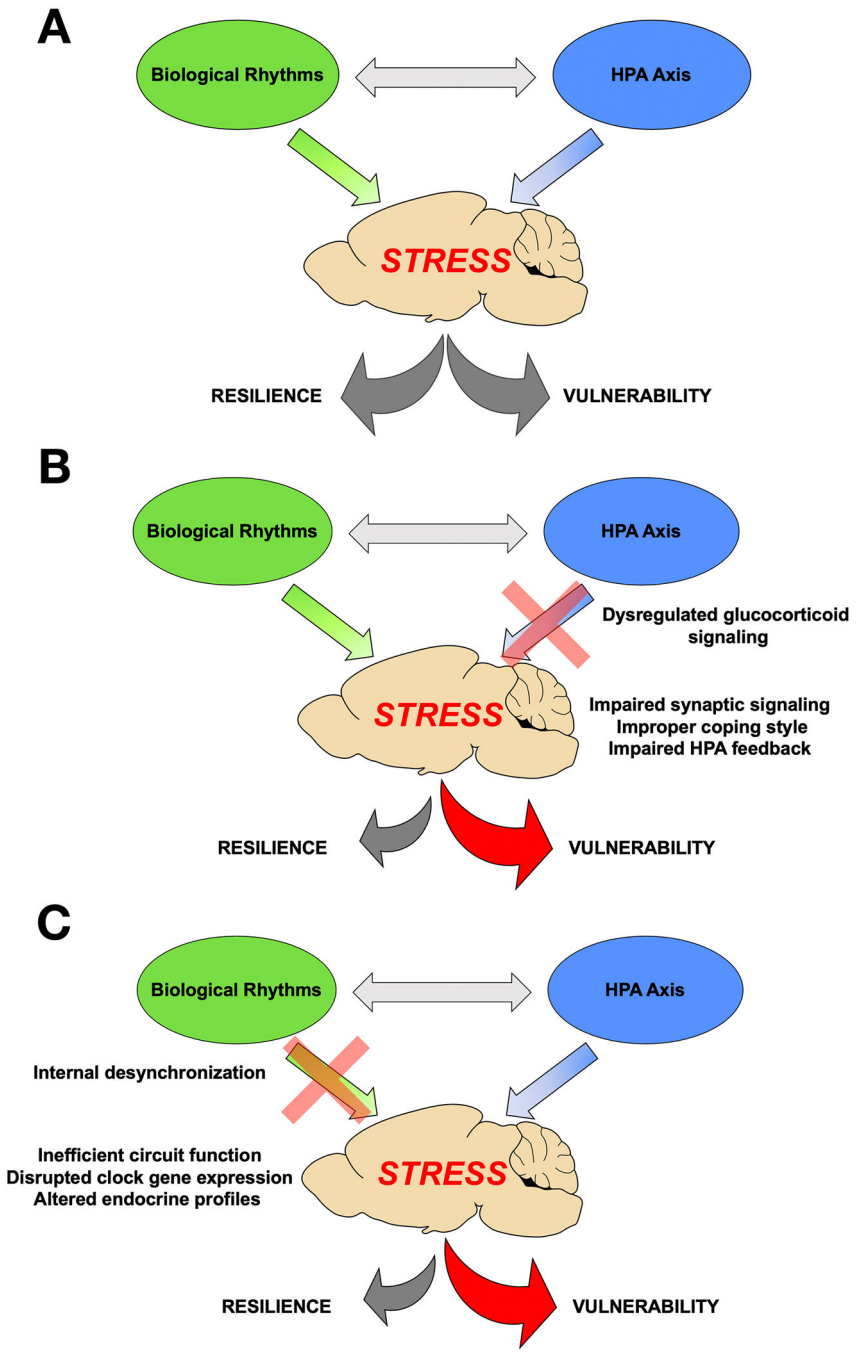

Figure 2. Hypothalamic Pituitary Adrenal Axis and Biological Rhythms interact to modulate neural, behavioral and physiologicla responses to stress.

Normally functioning HPA responses and biological rhythms promote balance in the neurobehavioral and physiological responses to stress (A). If HPA responses (B) or biological rhythms (C) are disrupted, then the balance can shift form resilience and healthy responses to vulnerability and pathological responses.