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Review article

The physiological significance of the circadian dynamics of the HPA axis: Interplay between circadian rhythms, allostasis and stress resilience

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ABSTRACT

Circadian time-keeping mechanisms preserve homeostasis by synchronizing internal physiology with predictable variations in the environment and temporally organize the activation of physiological signaling mechanisms to promote survival and optimize the allocation of energetic resources. In this paper, we highlight the importance of the robust circadian dynamics of allostatic mediators, with a focus on the hypothalamic-pituitary-adrenal (HPA) axis, for the optimal regulation of host physiology and in enabling organisms to adequately respond and adapt to physiological stressors. We review studies showing how the chronic disruption of circadian rhythms can result in the accumulation of allostatic load, which impacts the appropriate functioning of physiological systems and diminishes the resilience of internal systems to adequately respond to subsequent stressors. A careful consideration of circadian rhythm dynamics leads to a more comprehensive characterization of individual variability in allostatic load and stress resilience. Finally, we suggest that the restoration of circadian rhythms after pathological disruption can enable the re-engagement of allostatic mechanisms and re-establish stress resilience.

1. Introduction: allostasis, stress resilience and the importance of circadian timing

The term stress was initially used by Selye to define the body's non-specific response to any physical or psychological event, occurring as a result of a displacement from its internal physiological state (homeostasis) (Selye, 1956; Selye, 1998). Within this framework, stress-induced deviations from homeostasis are considered to be detrimental to host fitness, ultimately triggering various negative feedback mechanisms that restore physiological variables to their basal states (Ramsay and Woods, 2014). Thus, the term stress has become conventionally associated with negative connotations (McEwen, 2006). On the other hand, the mounting of an adequate stress response to various acute external threats is undoubtedly essential for host survival (McEwen, 2006). Recognizing this ambiguity, the concept of allostasis and allostatic load was introduced as an alternative hypothesis to explain the mechanisms through which homeostasis is maintained, while acknowledging both the protective as well as potentially physiologically detrimental effects of stress. Allostasis, defined as the "maintenance of stability through change" was proposed in an attempt to offer a more precise and integrated framework for understanding of physiological stressors, the host stress response and the regulation of physiological stress-adaptive processes (McEwen, 2003). Allostasis aims to expand upon the homeostatic framework, by differentiating between the essential (homeostatic) variables of physiology, which are maintained within a narrow physiological range for host survival, such as oxygen tension, pH etc. (referred to as homeostasis) and the mediators; various hormones, cytokines etc., which control these variables and are themselves more dynamically regulated so as to preserve homeostasis in a variable environment (McEwen and Wingfield, 2010). Thus, allostasis is associated with a labile equilibrium by which regulatory mediators actively deviate from basal levels to engage adaptive mechanisms in response to perceived stressors and consequently preserve or reestablish homeostasis after exposure to stress. Accordingly, transient stress-induced deviations of cortisol and other stress-responsive mediators from their basal dynamics followed by their timely return to pre-stress levels is considered to be beneficial by promoting host survival through the appropriate channeling of energetic resources for the activation of adaptive mechanisms (McEwen and Gianaros, 2010; Sterling, 2012). On the other hand, the chronic activation of such mediators results in the dysregulation of adaptive mechanisms, resulting in physiological 'wear and tear' or the accumulation of *allostatic load*, which reduces the

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ability of the host to flexibly cope with subsequent stressful perturbations (Ganzel et al., 2010; Juster et al., 2010; Schulkin, 2011).

The concepts of allostasis and allostatic load have also enabled a more nuanced understanding of mechanisms engaged in determining individual differences in the resilience and susceptibility to various physiological stressors (Karatsoreos and McEwen, 2011; McEwen et al., 2015). The notion of human stress resilience was initially formalized in child psychology studies conducted on individuals considered to be at high-risk for the development of psychological disorders (reviewed in Cicchetti, 2010). The discovery that some high-risk children did not develop psychopathology engendered great interest in identifying putative adaptive and maladaptive mechanisms that led to the differential psychological status of high-risk subjects who subsequently went on to develop psychiatric disorders and those who did not (Werner and Smith, 1992; Masten, 2001). Accordingly, resilience has been broadly defined as the maintenance of physiological, developmental and behavioral homeostasis through the activation of allostatic adaptive mechanisms in response to significant stress (McEwen, 2016; Pfau and Russo, 2015). A characterization of the allostatic mechanisms involved in mediating these adaptive responses is critical for an improved understanding of health and disease. Moreover, in addition to characterizing the mechanisms of adaptation it is critical to understand how the adaptation to a stressful event in itself influences the flexibility of the host to respond to subsequent novel challenges over its life course. The concepts of allostasis and allostatic load offer a framework of stress and host homeostasis that enables an improved characterization of both intra-individual variability in resilience over the life course of the host as well as inter-individual variability in resilience reflecting population level differences due to sex, ethnicity and underlying genetic differences (Karatsoreos, 2016).

Research in recent decades has begun to reveal that stress resilience involves the coordinated systemic interactions between numerous central (brain) as well as peripheral (body) signaling mechanisms (Pfau and Russo, 2015). As the principal mediators of allostasis, the key neuroendocrine stress-responsive signaling systems such as the hypothalamic-pituitary-adrenal (HPA) axis along with the sympathetic nervous system (SNS) mediate the cross-talk between the brain and rest of the body. Studies in both human and rodent models have shown that the HPA axis and SNS are critically involved in adaptation to stress, with their dynamics also influencing the flexibility of the host to novel challenges (Charney, 2004; Russo et al., 2012). Moreover, intra-individual and inter-individual differences in the dynamics of these systems are also considered to result in differences in stress resilience (Southwick and Charney, 2012).

In exploring how these physiological mechanisms are involved in the stress response, it is particularly important to acknowledge that the baseline homeostatic dynamics of these allostatic mediators are in fact regulated in a time-of-day dependent manner (Spencer et al., 2018). The maintenance of appropriate temporal relationships between the body's various physiological signaling systems enables the optimal allocation of energetic resources and the anticipation of predictable (daily) changes in the environment, thus promoting homeostasis (Riede et al., 2017). Such 24-hr periodic rhythms are governed by a hierarchically organized circadian system in which, the master pacemaker, located in the hypothalamic suprachiasmatic nucleus (SCN) synchronizes physiological and behavioral rhythms by regulating the rhythmic activity of various humoral and neuronal allostatic mediators (Buijs et al., 2003; Urbanski, 2011). Furthermore, multiple lines of evidence support the notion that the robust circadian dynamics of the modulators of allostasis are indicative of the ability of the host to flexibly respond and adapt to various physiological stressors (Karatsoreos and McEwen, 2014). In subsequent sections, the fundamental importance of circadian rhythms for the proper functioning of allostatic mechanisms is discussed [Fig. 1], with a specific focus on the HPA axis. We review studies that show how circadian desynchrony is representative of the accumulation of allostatic load and is associated with the pathological regulation of diverse physiological signaling systems. In doing so, we highlight the manner in which the host environment in a modern industrialized society contributes to the chronic disruption of the circadian dynamics of allostatic mediators, thereby compromising stress resilience. Moreover, we emphasize the importance of accounting for the basal circadian dynamics of allostatic mediators while attempting to pharmacologically manipulate their activity. Finally, we argue that the restoration of robust circadian rhythmicity through non-pharmacological means represents a promising approach by which the detrimental influence of the chronic demands imposed by modern society on human physiology might be minimized.

2. Neuroendocrine mediators of allostasis: the HPA axis mediates the cross-talk between brain and body

2.1. The HPA axis

The HPA axis is an intricately regulated signaling system essential for host survival and functions synergistically with the norepinephrine-releasing SNS to regulate the physiological stress response (Tsigos and Chrousos, 2002). The basal and stress-responsive activity of the HPA axis depends on a careful balance between its feedforward and feedback mechanisms. The stress response is initiated by a number of afferent neural pathways (6), eventually resulting in the release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the neuronal population in the hypothalamic paraventricular nucleus (PVN) into portal circulation. CRH and AVP bind to their respective receptors, CRH receptor 1, (CRHR1) and AVP 1B binding receptor (V1bR) in the pituitary, leading to the release of ACTH. Subsequently, systemic ACTH activates a signaling cascade upon binding to the melanocortin type 2 receptor in the adrenal glands, which eventually results in the de novo biosynthesis and release of glucocorticoids (Stephens and Wand, 2012). The principal glucocorticoid in humans is cortisol and that in most rodents is corticosterone. The glucocorticoids, in addition to their downstream physiological effects, also regulate their own synthesis by inhibiting the release of their precursors, CRH and ACTH, from the PVN and pituitary, respectively. Importantly, the glucocorticoid hormones exhibit pronounced circadian (~24 h) as well as ultradian rhythms (< 24 h; specifically, 1–2 hr periodic pulses for glucocorticoids), with practically all their physiological effects showing a robust time-of-day dependence (Spiga et al., 2014).

Glucocorticoids exhibit a diverse array of physiological effects from regulating metabolic and immune signaling, to influencing host behavior. Glucocorticoid signaling involves the binding of these steroid hormones to the glucocorticoid (GR) and mineralocorticoid (MR) receptors, respectively. Glucocorticoids have a 10-fold greater affinity for the MR in comparison to the GR, with the MRs exhibiting maximal occupancy at normal physiological concentrations of circulating glucocorticoids (Fuller et al., 2000). This differential receptor affinity accounts for the well-known biphasic and inverted U-shaped effects the glucocorticoids have on many downstream signaling elements (Mavroudis et al., 2015). Upon activation, the GR and MR translocate to the nucleus, where they function as transcriptional factors for a variety of gene expression products. GR and MR-activated mechanisms in various brain regions are also critically involved in mediating the negative feedback effects of circulating glucocorticoids on their precursors. Additionally, the PVN can also be inhibited by afferent brain regions such as the hippocampus and prefrontal cortex, which expresses high levels of GR (Herman, 2013; Radley and Sawchenko, 2011). In addition to the well-characterized receptor-mediated genomic effects there is an increased appreciation of non-genomic effects of glucocorticoids on physiological regulation (reviewed in Stahn and Buttgereit, 2008). The non-genomic effects of glucocorticoids occur much more rapidly and are mediated through putative G-protein coupled membrane receptors with a pharmacological profile that differs from that of the GR and MR receptors. Such non-genomic effects are

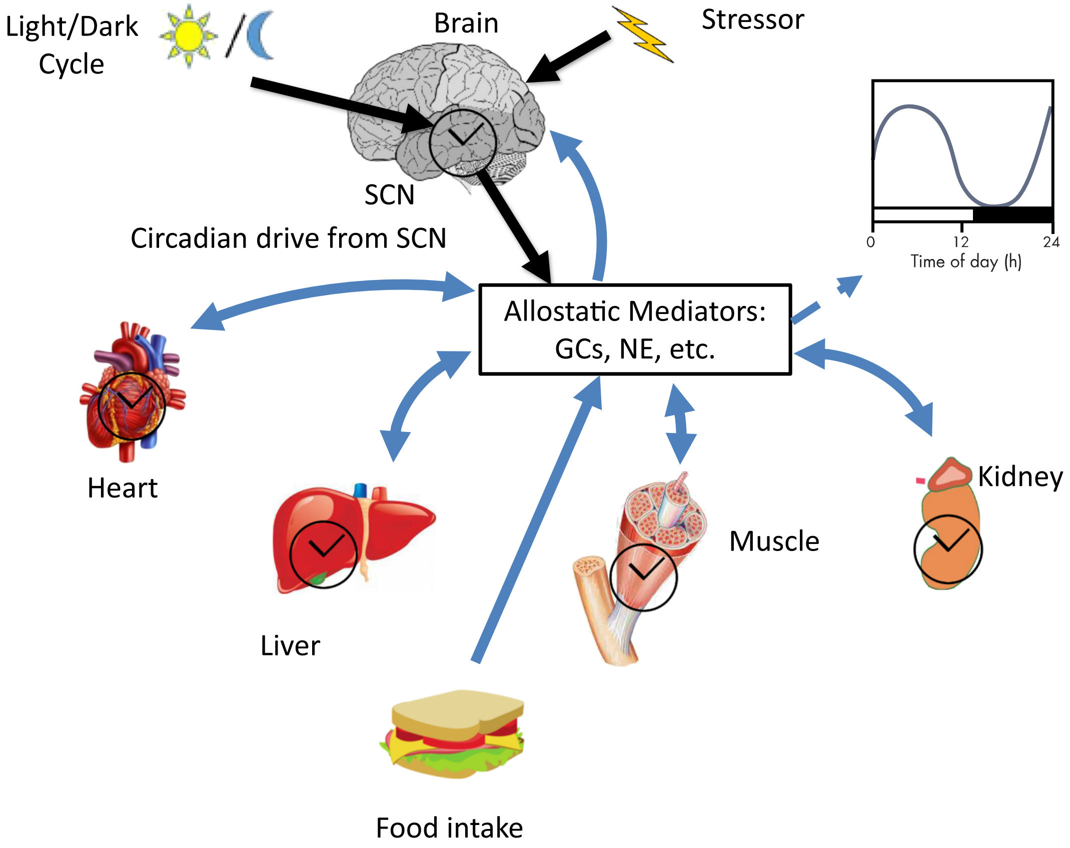

Fig. 1. The brain integrates environmental information; both predictable changes in the environment such as the light/dark cycle and food availability, as well as other unpredictable stressors. The central pacemaker in the SCN integrates environmental information and synchronizes internal physiological systems through the regulation of the allostatic mediators. Similarly, various brain centers are activated in response to acute stressors subsequently influencing the allostatic mediators, e.g. glucocorticoids (GCs) and norepinephrine (NE), and enabling the allostatic adaptation of various physiological signaling systems. The circadian dynamics of the allostatic mediators are critically involved in the optimal regulation of host physiology and in enabling organisms to adequately respond and adapt to physiological stressors. Partially adapted from Oster et al. (Oster et al., 2017).

thought to be important for rapidly relaying inhibitory signals to CRH and ACTH secretion (on the order of seconds to minutes) and have also been found to modulate glucocorticoid-responsive hypothalamic, hippocampal and amygdalar regions (Gjerstad et al., 2018; Groeneweg et al., 2011).

2.2. *Glucocorticoid actions in the brain and body*

2.2.1. *Glucocorticoid actions in the brain*

As the ultimate integrator of both physiological and psychological stressors, the brain orchestrates host behavior and physiology and is crucially involved in the dynamics of allostatic load accumulation and stress adaptation (McEwen and Gianaros, 2010). Studies on the effects of stress on the plasticity of various brain centers have revealed the importance of the optimal engagement of allostatic stress-responsive mechanisms such as the HPA axis. The hippocampus, responsible for short and long-term memory consolidation, was the first higher brain center discovered to express both MR and GR (McEwen, 1999). Accordingly, glucocorticoids exhibit biphasic effects on the excitability of hippocampal neurons, with MR activation increasing neuronal excitability and GR activation having opposite effects (de Kloet, 2014; ter Heegde et al., 2015). While acute stress-induced glucocorticoid increases can be associated with beneficial improvements in working memory and cognitive processing, chronic stress is associated with deficits in memory consolidation (de Kloet, 2014). Glucocorticoids have also been found to critically regulate the dynamics of cortical dendritic spine formation and elimination, which have important implications for the appropriate functioning of physiological learning and memory processes (Liston and Gan, 2011). In fact, dendritic spine formation and elimination dynamics are sensitive to circadian fluctuations in circulating glucocorticoid levels (Liston et al., 2013). Furthermore, glucocorticoid circadian rhythms are also strongly associated with levels of arousal; the rapid increase in glucocorticoid levels at the time of awakening is thought to promote cognitive activity together with the activation of peripheral metabolic pathways in the liver, adipose tissue and muscle, while their decline towards the end of the day is thought to facilitate sleep initiation (Oster et al., 2017).

The HPA axis mediators also interface with a diverse array of signaling moieties such as brain derived neurotrophic factor (BDNF) to exert complex effects on brain plasticity in response to stress (Jeanneteau et al., 2012). In addition to genomic effects, glucocorticoids also have rapid receptor-mediated non-genomic effects on neural architecture (McEwen, 2010). Apart from the hippocampus, other brain centers including the amygdala and prefrontal cortex have also shown to be sensitive to changes in levels of CRH and glucocorticoids. Studies have demonstrated marked plasticity in the neural architecture of these brain regions. For instance, reductions in hippocampal volume have been observed in a number of disorders that involve alterations in the activity of the HPA axis and other allostatic mediators, including major depression, post-traumatic stress disorder (PTSD), chronic inflammation, and Cushing's disease (Conrad, 2008).

2.2.2. *Glucocorticoid actions in peripheral tissues*

Glucocorticoids regulate a diverse array of signaling pathways in peripheral tissues. Importantly, the circadian variation in glucocorticoid levels is known to influence cardiovascular function and, together with catecholamines, maintain or increase blood pressure (Walker, 2007). Glucocorticoids are well-known for their influence on metabolic signaling pathways and were named for their ability to modulate glucose metabolism, where they function to increase blood glucose levels by upregulating gluconeogenic activity (Christiansen et al., 2007). Glucocorticoids also regulate lipid deposition and can stimulate the maturation of adipocytes (Macfarlane et al., 2008). Moreover, they stimulate protein degradation and can thus, further support gluconeogenic activity through the production of pyruvate. Therefore, basal and stress-induced changes in glucocorticoid levels can influence adiposity and muscle degradation in supporting the energetic requirements of the host and can also influence metabolic hormones, such as ghrelin (Otto et al., 2004) and leptin (Sominsky and Spencer, 2014), which are involved in regulating appetite and the energetic balance of the host. Glucocorticoids are also well-known for their anti-inflammatory effects and inhibit a number of immune processes, including the production of various proinflammatory cytokines (Coutinho and Chapman, 2011; Foteinou et al., 2009).

Finally, many of these peripheral processes in turn influence cognitive and stress-responsive circuits in the brain, thereby creating an intimate bidirectional link between the various glucocorticoid dependent processes (Pfau and Russo, 2015; Pierre et al., 2017). For example, cytokines secreted by peripheral blood mononuclear cells can influence the central nervous system via stimulation of the vagus nerve (Pavlov and Tracey, 2012) as well as via humoral pathways by crossing over the blood-brain barrier; subsequently affecting the activation of the HPA axis, and various neural circuits in the brain including the basal ganglia and anterior cingulate cortex, which can lead to changes in motor activity, arousal and anxiety (Miller et al., 2013). Moreover, metabolic hormones such as leptin, secreted by adipose tissue and ghrelin, secreted by the stomach, participate as afferent signals to brain centers such as the hypothalamus, and thereby modulate physiological processes involved in the regulation of energy homeostasis (Dieguez et al., 2011; Howick et al., 2017; Park and Ahima, 2015).

3. Circadian rhythms and the mediators of allostasis

Practically all mediators of allostasis exhibit pronounced circadian variation in their activity. The circadian variability of these mediators is believed to enable the host to optimize its physiology and behavior by actively anticipating predictable periodic changes in the environment, thereby conferring improved fitness in comparison to a host that passively responds to a changing environment (Karatsoreos and McEwen, 2014). Moreover, the circadian gating of various signaling cascades also allows for the optimal temporal separation of physiological processes that are chemically, energetically or behaviorally incompatible.

The circadian system in mammals is organized into a hierarchical network of interconnected molecular clocks with a master clock located in the hypothalamic suprachiasmatic nucleus (SCN) and peripheral molecular clocks within the cells in various tissues and organs (Buijs et al., 2003; Dibner et al., 2010). Circadian rhythms are primarily orchestrated by the rhythmic firing of neurons in the SCN and are entrained mainly to the light/dark cycle along with diurnal variation in temperature. Upon integrating environmental phase information, the SCN synchronizes the network of peripheral circadian clocks through the rhythmic secretion of allostatic mediators of the HPA axis and the autonomic nervous system, the glucocorticoids and norepinephrine (Cutolo and Masi, 2005; Edery, 2000).

Both the master-clock in the SCN and the peripheral circadian clock share a common molecular architecture, composed of a cell-autonomous transcriptional autoregulatory feedback loop (Takahashi, 2017). The activators of the mammalian circadian network are the CLOCK and BMAL1 transcription factors, which form a heterodimeric complex (Gekakis et al., 1998). The CLOCK-BMAL1 complex binds to E-box containing regulatory elements in a set of rhythmically expressed genes for the repressor proteins period (PER) and cryptochrome (CRY), which inhibit the expression of CLOCK-BMAL1 in turn (Shearman et al., 2000).

3.1. *Bidirectional regulation of the HPA axis and circadian rhythms*

Research over the past decade has revealed much evidence for a strong bidirectional link between the stress-responsive HPA axis and circadian clock machinery (Nicolaides et al., 2017). The cross-talk between the two influences not only basal activity of diverse physiological signaling systems but also the flexibility to adapt to stressful changes in the environment (Koch et al., 2017).

3.1.1. *Influence of the circadian clock on glucocorticoids*

Together with peripheral circadian clocks the SCN coordinates glucocorticoid circadian rhythms at multiple regulatory loci in the HPA axis (Butler et al., 2010; Spiga et al., 2014). The SCN directly regulates glucocorticoids circadian rhythms through neuronal projections in the hypothalamic PVN, thereby relaying photic information to the HPA axis, and causing its activity to peak during the active phase; during the day in humans and other diurnal species, and at night in nocturnal species (Kalsbeek et al., 2012; Kalsbeek et al., 1996). The SCN also modulates the sensitivity of the adrenal cortex to ACTH in a time-of-day dependent manner through what is believed to be an extra-pituitary autonomic pathway (Chung et al., 2011). Recent evidence also suggests that a peripheral circadian clock localized in the adrenal cortex further modulates the circadian secretion of the glucocorticoids (Oster et al., 2006; Son et al., 2008). Moreover, the CLOCK-BMAL heterodimer in peripheral blood mononuclear cells has been found to regulate GR transcriptional by modulating the time-of-day dependent acetylation of the receptor, thereby reducing its transcriptional efficiency and introducing a further layer of control by modulating the glucocorticoid sensitivity of the target tissue in a time-of-day dependent manner (Charmandari et al., 2011; Nader et al., 2009). CRY1 and CRY2 are also able associate with GR in a hormone-dependent manner and alter the global transcriptional response to glucocorticoids (Lamia et al., 2011). Taken together, these studies suggest that the circadian clock imposes multiple layers of control in order to influence both the rhythmic secretion of circulating glucocorticoids as well as the response of glucocorticoid-sensitive target tissues in a time-of-day dependent manner.

In addition to regulating the basal dynamics of glucocorticoid secretion, the circadian clock also modulates the stress-responsive behavior of the HPA axis in a time-of-day dependent manner. A number of studies have attempted to characterize the diurnal variation of the HPA axis' response to a variety of stressors. In general, the HPA axis is found to be more responsive towards the end of the active phase or during the inactive phase, when glucocorticoid levels are low, in comparison to when basal glucocorticoids are high, during the active phase (Bernatova et al., 2002; Pollmacher et al., 1996; Retana-Marquez et al., 2003). While the underlying mechanisms governing such time-of-dependent glucocorticoid responses to stress are yet to be completely elucidated, studies have found that a gating of the sensitivity of the adrenals to ACTH by the local adrenal circadian clock (Oster et al., 2006; Son et al., 2008) as well as through autonomic splanchnic nerve innervation (Ulrich-Lai et al., 2006) can contribute to this phenomenon. Furthermore, the circadian dynamics of the HPA axis can also influence ability of the host to successfully adapt to stressors in a complex manner. Studies using animal models of chronic psychosocial stress have found that mice repeatedly exposed to stressors during their active phase (during the night), showed reduced HPA axis activity and altered metabolic activity (Bartlang et al., 2012; Bartlang et al., 2014), while mice stressed during the inactive phase showed minimal stress-related physiological alterations. Interestingly, using a “two-hit” stress model Johnson et al. (2003) found that rats exposed to prior stress caused a sensitization of the HPA response to a novel stressor, when the novel stressor was applied during the inactive phase rather than in the active phase.

3.1.2. Influence of glucocorticoids on the circadian clock

On the other hand, glucocorticoids have been found to reset the activity of peripheral circadian clock gene expression through receptor-mediated mechanisms in diverse tissues including the liver, kidney and heart (Balsalobre et al., 2000). Interestingly, while studies have found that glucocorticoids are able to directly influence the phase characteristics of the canonical *Per* genes in peripheral tissues, rhythmic expression in the SCN itself appears to be insensitive to the direct actions of glucocorticoids (Nicolaides et al., 2017). Accordingly, the SCN has been found to exhibit little to no glucocorticoid receptor expression (Rosenfeld et al., 1988; Segall et al., 2009). Evidence suggests that basal glucocorticoid circadian rhythms promotes the robust circadian rhythmicity of peripheral clock genes and contributes to the maintenance of appropriate phase relationships between the SCN and the peripheral tissues as well as between the various peripheral tissues as well. Adrenalectomy, the surgical removal of the adrenals, has been found to result in the disruption of *Per1* and *Per 2* rhythms in a variety of tissues in rodent studies (Su et al., 2015), including in adipose tissue (Su et al., 2015), liver (Pezuk et al., 2012) and the kidney (Pezuk et al., 2012). In addition to influencing the circadian machinery in myriad peripheral target tissues, glucocorticoids have also been found to impact clock rhythmicity in the higher brain centers implicated in the adaptive response to stressors, including the amygdala and hippocampus (Conway-Campbell et al., 2010; Segall et al., 2009). Moreover, the administration of synthetic glucocorticoids such as dexamethasone and prednisolone have been found to augment the amplitude and reset the phase of circadian gene expression in adipocytes (Barnea et al., 2013), lung epithelial cells (Burioka et al., 2005), and bone (Fujihara et al., 2014). Recent studies have also shown that stress-induced secretion of glucocorticoids is able to reset peripheral circadian clock rhythms (Nader et al., 2009). Thus, given the intricate bidirectional influences between the circadian clock and the stress-responsive HPA axis, alterations in either system can have substantial effects on the physiological functioning of the other.

3.2. Disrupted circadian rhythms are indicative of allostatic load accumulation and compromised stress resilience

Circadian rhythms directly influence the systemic regulation of metabolic, immune (Cermakian et al., 2014), hormonal (Buijs et al., 2003), and cardiovascular functions (Lemmer, 2006). The chronic disruption of homeostatic circadian rhythmcity increases the susceptibility to systemic inflammatory and metabolic disorders (Cermakian et al., 2014; Takahashi et al., 2008) suggesting an important protective role for circadian rhythms. Accumulating evidence suggests that a robustly functioning circadian system underpins the appropriate functioning of allostatic mediators and the capacity for resilient allostatic adaptation.

There is an increasing appreciation for adverse health effects of modern lifestyles entailing increased sleep deprivation, misalignment of the circadian clock with the light/dark cycle during shift work and transmeridian air travel, as well as increased exposure to light at night (Fonken and Nelson, 2014). A number of studies in animal models have found that chronic circadian disruption is associated with pathological dysregulation of a number of critical physiological signaling systems, including metabolic, immune and neurobehavioral pathways (Karatsoreos, 2014; West and Bechtold, 2015). In a mouse model of circadian disruption, Karatsoreos et al. showed that exposing mice to a 20 hr light/dark, thereby preventing the entrainment of their endogenous circadian system to the environment, resulted in physiologically profound alterations in metabolic activity, neural architecture in the brain, and behavioral changes (Karatsoreos et al., 2011). Chronic circadian misalignment in these animals resulted in an increase in weight gain, obesity, and disruptions in metabolic hormones. Furthermore, circadian misalignment also substantially altered the cytokine response to an immune stressor. A similar experimental protocol used to study the effects of circadian disruption in humans in controlled laboratory conditions found that circadian misalignment also resulted in adverse metabolic effects; an inversion in cortisol circadian rhythms was associated with increased glucose levels and blood pressure, and decreased insulin sensitivity and sleep efficiency (Scheer et al., 2009).

Chronic circadian disruption is also strongly correlated with neurobehavioral changes. In the above mentioned study by Karatsoreos et al. (2011), circadian misalignment in mice also resulted in decreased complexity of neurons in the prefrontal cortex, the brain center involved in executive and emotional control, and reductions in cognitive flexibility. Interestingly, even short-term circadian desynchrony has been shown to disrupt memory consolidation in response to fear-conditioning, thus suggesting that even relatively brief periods of circadian misalignment could compromise stress resilience (Loh et al., 2010). A study by Cho et al. showed that flight crew workers exhibited higher cortisol levels and that workers with prolonged (> 5 years) elevated cortisol levels also had smaller medial temporal lobes, and cognitive deficits in tasks testing visual-spatial and memory performance (Cho, 2001). Moreover, epidemiological studies have shown that shift workers are at a greater risk for developing various disorders including depression, obesity, cancer and diabetes (Stevens and Zhu, 2015; Wang et al., 2011).

The disruption of HPA axis circadian rhythmicity is associated with pathophysiological implications. The maintenance of appropriate homeostatic circadian rhythmicity in the HPA axis is not only necessary for mounting an adequate response to stressors but also for the appropriate physiological regulation of glucocorticoid-sensitive target tissues across the body (Koch et al., 2017; Oster et al., 2017; Spiegel et al., 1999). Disruption of glucocorticoid rhythms has been shown to impair the ability of the HPA axis to appropriately terminate stimulus-induced ACTH secretion (Jacobson et al., 1988). It is hypothesized that the repeated inappropriate engagement of the HPA axis in response to chronic or repeated stressors (i.e. either inadequate or excessive activation of the HPA axis) results in physiological wear and tear (Karatsoreos and McEwen, 2011). Though it has generally been difficult to determine a causative role for circadian misalignment and HPA axis disruption in the pathophysiology and symptomatology of psychiatric disorders, an increasing number of studies have found an association between the prevalence of disrupted HPA axis circadian rhythmicity and the incidence and severity of chronic stress-related psychiatric disorders including major depression (Keller et al., 2017), bipolar disorder (Fries et al., 2014) and PTSD (de Kloet et al., 2006). Moreover, circadian disruption is also thought to lead to the exacerbation of such diseases (Karatsoreos, 2014). Studies in humans have found that chronically stressed individuals are more likely to have a dampened cortisol rhythm, with elevated nocturnal glucocorticoid levels (Ahima et al., 1998; Spies et al., 2014). This nocturnal elevation of the circadian trough of the cortisol rhythm is hypothesized to cause a shift of the MR-GR balance, with an excessive activation of MR-dependent mechanisms, and is found to be a risk factor for obesity (Hoppmann et al., 2010), insulin resistance (Hoppmann et al., 2010) and memory deficits (Harris et al., 2013). Studies using animal models find that appropriately regulated circulating glucocorticoid oscillations are important for learning and memory processes by regulating synaptic formation and maintenance. An important study by Liston et al. showed that a robust circadian glucocorticoid peak promoted dendritic synapse formation in the mouse cortex after motor skill learning, while glucocorticoid troughs were involved in the maintenance of spines and long-term memory retention. On the other hand, chronic, excessive exposure to glucocorticoids, suggestive of disrupted glucocorticoid rhythms, eliminated new learning-associated spines through MR-dependent transcriptional mechanisms and also disrupted previously acquired memories (Liston et al., 2013).

In addition to misalignment with the light-dark cycle, peripheral circadian clock disruption might also result from irregular meal patterns due to social mismatch (Arble et al., 2009; Chakradeo et al., 2018). Importantly, since the HPA axis also interfaces with critical metabolic signaling pathways, irregular meal patterns can often also cause disruption of HPA axis activity. For instance, individuals with night-eating-syndrome, where > 20% of the caloric intake occurs after the evening meal, exhibit dampened circadian amplitudes for cortisol, insulin, and ghrelin (Birketvedt et al., 2002). Disrupted cortisol rhythms have also been found in the patients with anorexia nervosa and bulimia nervosa (Ferrari et al., 1990; Herpertz et al., 2000; Monteleone et al., 2000). Moreover, these patient groups also have an increased prevalence of depression compared to the general population (Mischoulon et al., 2011), suggesting that disturbances in the homeostatic dynamics of the circadian clock and the HPA axis could lead to dysregulation of neurobehavioral and stress-resilient circuits and vice-versa.

Taken together, these studies further underscore the physiological significance of the close connection between the circadian and stress systems mediated through the allostatic signaling systems such as the HPA axis. Therefore, circadian disruption of the stress-axis can profoundly influence the adaptive functioning of allostatic mediators, resulting in allostatic overload and undermining the allostatic mechanisms responsible for promoting adaptation to environmental challenges. Continual circadian desynchrony can eventually lead to changes in neural architecture and behavior, thereby causing long-term maladaptive changes in stress-responsive circuits and increasing susceptibility to the development of systemic diseases including metabolic, immune and psychiatric disorders. Given the bidirectional interactions between the allostatic mediators and the circadian clock, chronic engagement of the stress-responsive circuits could also result in severe circadian disruption, prompting a vicious cycle of systemic dysregulation. It is interesting to note that patients with diseases such as rheumatoid arthritis (Cutolo and Straub, 2008), cancer (Savvidis and Koutsilieris, 2012), and Type I diabetes (Kalsbeek et al., 2014) frequently exhibit disrupted circadian rhythms. Interestingly, circadian disturbances in allostatic mediators is often associated with a poorer prognosis of systemic diseases such as breast cancer (Savvidis and Koutsilieris, 2012; Stevens, 2005). Moreover, such chronic diseases are often associated with the incidence of comorbidities such as depression, asthma, and cardiovascular disease (Dougados et al., 2014; Garcia-Olmos et al., 2012).

4. Intraindividual and interindividual variability in circadian rhythms, allostasis and stress resilience

Within the allostatic framework, individual variability in resilience may be further characterized in terms of a) intra-individual variability – changes in stress resilience that occur throughout the entire lifespan of the host, and b) inter-individual variability – arising as a result of sex differences and underlying genetic differences.

4.1. Variability over the life course

Normal physiological aging is accompanied by a number of changes to the HPA axis and circadian timing system (Gaffey et al., 2016). In general, a dampening of the circadian amplitude of the SCN and the HPA axis is observed with advancing age (Li and Satinoff, 1995; Satinoff et al., 1993; Van Cauter et al., 1996). The dampening in the circadian rhythm of the SCN in older adults is correlated with neuronal degeneration in the SCN and is often associated with earlier sleep timing, reduced sleep consolidation and increased sleep disturbances (Duffy et al., 2015). These changes in sleep dynamics are further accompanied by a phase advance in circadian rhythmicity during aging (Duffy et al., 2015). In the case of the HPA axis, the dampening of the circadian amplitude is usually accompanied by a progressive increase in the circadian nadir concentrations of cortisol with age, which might lead to an increase in overall systemic cortisol exposure (Vgontzas et al., 2003). Furthermore, aging is also associated with a hyperactivation of the HPA axis as well as a decrease in the strength of negative feedback of the glucocorticoids on their precursors, CRH and ACTH in humans and non-human primate models (Goncharova, 2013). In general, these changes in the stress-responsive HPA axis and the circadian timing system are positively correlated with negative health outcomes, with clinical studies indicating a higher risk for anxiety and stress-related disorders, cardiovascular disease, and decreased immunity (Hood and Amir, 2017a, 2017b; Mattis and Sehgal, 2016). In one of the largest studies to date, amongst healthy elderly patients followed over a 4-year observation period, the individuals exhibiting a progressive increase in cortisol levels over the observation period and with higher basal cortisol levels showed cognitive deficits (Lupien et al., 1994). Moreover, these individuals were also found to have smaller hippocampal volumes in comparison to age-matched controls who did not exhibit the progressive rise in cortisol levels over the study period. Thus, while causal relationships are yet to be established, one can hypothesize that the changes in the regulation of the HPA axis and other allostatic mediators that occur during aging diminish stress resilience and predispose the host to the development of chronic-stress disorders.

The HPA axis along with other stress-responsive signaling mechanisms is also strongly influenced by early-life stressful experiences. In animal models, it is well-established that unpredictable prenatal stress causes the HPA axis and the ANS to have increased stress-reactivity, which is conserved over the entire lifespan of the organism (Weinstock et al., 1998; McEwen, 2002). On the other hand, postnatal stress is found to counteract the effects of prenatal stress and eventually result in the reduced stress-reactivity of the HPA and ANS (McEwen, 2002). In a study by Yehuda et al., infant offspring of mothers who were pregnant when exposed to trauma, had lower than normal cortisol levels (Yehuda et al., 2005). Studies have found that low cortisol levels are associated with an increased risk for PTSD development (Yehuda and LeDoux, 2007) thus, suggesting that prenatal stress might contribute to the endocrine alterations that could influence resilience to stressors later in life. Clinical studies have found that early-life stress is also associated with cognitive deficits (Lupien et al., 1994) and the subsequent development of enhanced anxiety and depressive symptoms (Fonzo et al., 2016; Juruena, 2014). Moreover, early-life stress-induced alterations in the circadian regulation of the HPA axis have also been suggested to contribute to metabolic derangements that have been observed to occur later in life (Maniam et al., 2014). Such developmental changes in the plasticity of the HPA axis and glucocorticoid sensitive networks are hypothesized to be an important contributor to the inter-individual differences in stress resilience observed later in life, including the differential effects of aging and susceptibility to chronic stress disorders.

4.2. Sex differences in circadian rhythms and allostatic regulation

Substantial sex differences exist in the regulation of the HPA axis and the circadian timing system, with implications for allostatic stress resilience. The differential influences of the gonadal hormones, estrogen and testosterone are thought to be the primary factors in determining sex differences in physiological signaling (Bailey and Silver, 2014). Studies have found sex differences in morphology, electrical activity and peptide levels in the SCN (Kuljis et al., 2013). In humans, the rostrocaudal axis of the female SCN was found to have a greater volume and length in comparison to males (Hofman et al., 1988). The SCN is known to receive both estrogenic and androgenic inputs, with sex differences in the relative expressions of estrogen (ER) and androgen receptors (AR), respectively (Fernandez-Guasti et al., 2000; Kruijver and Swaab, 2002). In humans, the female SCN expresses much greater amounts of ERα (Kruijver and Swaab, 2002). Moreover, in general the intrinsic circadian period in women has been found to be shorter than in men (Duffy et al., 2011). With respect to the HPA axis, studies in animals have found that the basal glucocorticoid circadian rhythmicity in females is much more pronounced with higher peak levels than in males; varies with the phase of estrous cycle and is correlated with circulating estrogen levels (Atkinson and Waddell, 1997; Goel et al., 2014). In general, androgens have been found to have an inhibitory influence on the HPA axis and its stress reactivity while estrogens have been found to have an excitatory influence (Goel et al., 2014; Seale et al., 2004). Such differences in the underlying dynamics of the circadian timing system and allostatic mediators are manifest in differences in the prevalence of disease, sleep homeostasis and stress susceptibility (Bailey and Silver, 2014; Santhi et al., 2016). Of the diseases that are associated with HPA axis dysfunction, women are generally more prone to the development of autoimmune disease such as rheumatoid arthritis, while men are more prone to infectious diseases (van Lunzen and Altfeld, 2014; Whitacre, 2001). Furthermore, women are more likely to exhibit a morning chronotype in comparison to males and have also been found to more rapidly accumulate sleep debt in response to sleep deprivation (Mong et al., 2011). Differences in the accumulation of the sleep debt could make women more susceptible to the detrimental effects of circadian desynchrony in response to shift work and jet lag. In fact, clinical studies have found that cognitive impairment in response to circadian misalignment was greater in women than in men (Armitage et al., 2001; Mong et al., 2011).

5. The significance of chronotherapeutic manipulation of allostatic mediators

5.1. Lessons from the chronopharmacological administration of synthetic glucocorticoids

Synthetic glucocorticoids are widely used for their immunosuppressive and anti-inflammatory properties. A little over 1% of the U.S. population is estimated to use oral glucocorticoids on a regular basis (Overman et al., 2013). The administration of synthetic glucocorticoids is often associated with the incidence of side effects due to the exposure to supraphysiological doses (Liu et al., 2013). Patients undergoing glucocorticoid therapy have a greater risk of developing depression, anxiety, metabolic disturbances and have a greater incidence of cognitive deficits (Ciriaco et al., 2013; Oster et al., 2017; Schäcke et al., 2002). Moreover, withdrawal from long-term glucocorticoid therapy is often accompanied by adrenal insufficiency, and the associated adverse health effects, as a result of the suppression of endogenous glucocorticoid production due to the potent negative feedback effects of the synthetic glucocorticoids on the HPA axis (Krasner, 1999). Chronic exposure to supraphysiological doses of synthetic glucocorticoids can result in the dysregulation of many of the same allostatic mechanisms observed in chronic stress disorders, such as an imbalance in the relative activation of MR and GR-dependent mechanisms, a desensitization of glucocorticoid sensitive neuronal networks and associated changes in neurobehavioral signaling (de Kloet, 2014). It should be noted that while most commonly used synthetic glucocorticoids such as dexamethasone and prednisolone do no exhibit high blood-brain barrier permeability, it is hypothesized that the suppression of endogenous glucocorticoid secretion due to the inhibition of the HPA axis, could lead to a hypocortisolemic state in the brain (Oster et al., 2017).

The disruption of endogenous cortisol circadian rhythmicity is suggested to be an important causal factor in the development of adverse effects associated with the long-term use of synthetic glucocorticoids. There has been great interest in the development of novel dosage forms that enable control over the dose and timing of administration so as to preserve the endogenous cortisol circadian rhythm while still maintaining the therapeutic benefits of synthetic glucocorticoid administration. The degree of suppression of the endogenous cortisol rhythm is found to have a strong time-of-day dependence. In general, the administration of synthetic glucocorticoids in the evening, near the nadir of the cortisol rhythm, is found to have the maximal suppressive effect on the endogenous rhythm, while administration during the rising phase of the cortisol rhythm has been found to have decreased suppression (Arvidson et al., 1997; Liu et al., 2013). Importantly, in diseases such as asthma (Burioka et al., 2010) and rheumatoid arthritis (Buttgereit et al., 2015) where disease symptoms exhibit a prominent circadian dependence, appropriate chronopharmacological administration of glucocorticoids can provide maximal treatment efficacy while also mitigating the adverse effects associated with chronic glucocorticoid overexposure. As such, the use of a modified-release formulation of low-dose prednisone, developed for the administration of the drug around bedtime (10 PM) such that it is released 4 h later (~2 AM) was found to cause minimal disruption of HPA axis activity in RA patients and minimize the incidence of reported side effects, while still maintaining anti-inflammatory efficacy (Kirwan, 2011; Kirwan et al., 2006). Interestingly, a study involving these patients found that administration of a 8-week course of the modified-release prednisone, in fact, augmented the cortisol circadian rhythm, as well as increased the glucocorticoid response to CRH stimulation (Kirwan, 2011). These observations suggest that long-term chronopharmacological dosing of glucocorticoids can cause adaptive regulatory changes in the HPA axis that influence both its basal and stress-responsive characteristics (Rao et al., 2018). In addition to minimizing the suppression of the HPA axis, chronopharmacological dosing of glucocorticoids was also found to minimize the phase disruption of the peripheral circadian clocks (Hayasaka et al., 2007; Honma et al., 2015).

In general, chronic-stress related psychiatric disorders such as depression, anxiety and PTSD are considered to arise due a pathological loss of resilience. Various pharmacological agents such as serotonin and noradrenergic re-uptake inhibitors are used along with targeted behavioral therapies to re-engage disrupted allostatic mechanisms and promote resilience (Griffin et al., 2014). Recently there has been an increased interest in the administration of the exogenous glucocorticoids in some patients with PTSD (de Quervain and Margraf, 2008). The rationale for this approach was based on the finding that individuals with glucocorticoid levels close to the lower end of the physiological limit were predisposed to development of PTSD symptoms (Yehuda and LeDoux, 2007). Low-dose cortisol treatment in PTSD patients over a 3-month observation period was found to reduce PTSD symptoms, without causing adverse effects. Interestingly, in another pilot study Zohar et al. found that high-dose hydrocortisone treatment within 6 h of a traumatic experience in subjects presenting with acute stress symptoms resulted in a significantly more favorable post-traumatic symptom trajectory and decreased the risk of PTSD development (Zohar et al., 2011). The therapeutic benefit of glucocorticoids is attributed to a decrease in (aversive) memory retrieval through the glucocorticoid-induced inhibition of temporal lobe activity (Aerni et al., 2004; de Quervain and Margraf, 2008; Schelling et al., 2004), glucocorticoid-dependent modulation of spine density in the amygdala (Rao et al., 2012), dentate gyrus and increased levels of BDNF (Zohar et al., 2011). Nonetheless, the ultimate therapeutic benefits of exogenous glucocorticoid administration for their palliative or symptom-relieving effects in PTSD must be investigated further in larger controlled clinical trials. Taken together, the above studies support the notion that the appropriate pharmacological manipulation of critical allostatic mediators by considering the time-of-day dependent basal dynamics of these mediators as well as appropriately targeting specific patient populations can provide therapeutic benefit while minimizing the incidence of systemic side-effects (Hartmanshenn et al., 2016).

5.2. Nonpharmacological engagement of circadian mechanisms to restore resilience

Given that the circadian clock together with the HPA axis interfaces in a bidirectional manner with multiple physiological signaling systems, the re-alignment and/or augmentation of circadian rhythms can enhance allostatic adaptive resilience and can be used as an effective therapeutic strategy for some chronic systemic disorders (Rao et al., 2016). As discussed in the previous section, pharmacological therapies target specific mediators involved in the disease process in order to reverse disease symptoms by aiming to restore these variables from a perturbed "diseased" state to a homeostatic "healthy" state. However, the restoration of a single or a handful of "diseased" allostatic variables through such pharmacological therapy often does not alleviate allostatic load completely, since the pathophysiology of chronic-stress disorders is often systemic in nature, involving multiple allostatic mediators and adaptations in allostatic mechanisms spanning multiple physiological levels, and occurring over time-scales that widely differ from those at which the relatively "acute" pharmacological treatments operate. In such cases, it has been argued that non-pharmacological approaches that non-specifically engage with multiple allostatic mediators at a systemic level might represent a promising therapeutic strategy (McEwen et al., 2015).

Individuals with psychiatric disorders who frequently present with sleep and circadian disturbances often respond well to various forms of behavioral therapy (Sarris et al., 2014). The aim of such behavioral strategies is to modulate the daily activity routines of the patient so as to establish behavioral patterns that are more closely aligned with the natural light/dark cycle (Asarnow et al., 2013; Hickie et al., 2013). Such a strategy relies heavily on self-monitoring and strict adherence to specific waking and sleeping schedules. The incorporation of regular physical activity into these approaches can further improve adherence to sleep/wake routines and has been shown to augment symptomatic benefits (Garfield et al., 2016). Physical activity by itself has also been found to have potent anti-depressive effects (Childs and de Wit, 2014; Sarris et al., 2014). At a physiological level, physical activity not only benefits the cardiovascular and metabolic systems but also has cognitive benefits by improving executive functioning (McEwen, 2013). While the results are mixed, some studies suggest that physical activity can also modulate circadian phase and be an effective entrainer of circadian rhythms (Atkinson et al., 2007; Yamanaka et al., 2006).

Light therapy, a more explicit non-pharmacological approach for the treatment of chronic-stress related disorders, has received much attention for its antidepressant effects (Terman and Terman, 2005). This strategy involves a modality with natural chronobiological significance and aims to modulate the phase and amplitude characteristics of the master circadian clock in the SCN. Exposure to bright light (especially the short blue to green wavelengths) during the day and dim light at night in generally is found to advance the phase of the circadian clock while exposure to bright light in the evening and dim light in the morning delays the circadian phase (Hickie et al., 2013). Given that circadian disruption in chronic-stress disorders might also occur due to a phase mismatch between the central, SCN and peripheral oscillators, light therapy coupled with behavioral therapy has also been used for improved therapeutic benefit. Interestingly, a wealth of recent evidence shows that behavioral interventions such as time-restricted feeding can specifically reset the peripheral circadian oscillators uncoupling them from the SCN (Bae and Androulakis, 2017; Longo and Panda, 2016). While the modulatory effects of time-restricted feeding on the metabolic and immune systems are well supported by experiment, the benefits of time-restricted feeding for re-establishing resilience in chronic-stress related disorders such as depression, anxiety and PTSD are yet to be established.

Finally, it is worth mentioning that certain non-pharmacological therapies such as exposure therapy for conditions such as PTSD while not modulating the circadian rhythms directly do show a time-of-day dependence in their efficacy. Exposure therapy involves the repeated introduction of specific cues that are associated with a traumatic event in order reduce the fear responses triggered by the cues over time. Intriguingly, exposure therapy is found to be more efficacious when administered during the morning compared to the evening (Meuret et al., 2016; Pace-Schott et al., 2013).

6. Towards a more quantitative characterization of allostasis through mathematical modeling

While considerable progress has been achieved in determining the effects of stress on a variety of stress-responsive physiological systems – the HPA axis, SNS, the metabolic and immune systems – and the functioning of the brain and various peripheral organs, a number of important issues are yet to be resolved. An important challenge deals with integrating the influence of stressors across multiple physiological scales – from the molecular and cellular level, to neural circuits, to the interactions between physiological systems and eventually to ecological effects at the population level. It has been suggested that such an integration of stress responses across these multiple scales will result in a different conceptual model of physiological stressors and the stress response (Romero et al., 2015). Another key challenge involves obtaining an improved characterization of allostatic load and overload during chronic activation of the stress response. While the energetic requirements of the host are generally considered to be the most critical variable in determining overall allostatic load, such a variable is generally experimentally impractical to determine (Romero et al., 2009). Instead glucocorticoids have usually been used as an indicator of internal energetic state. However, the regulation of glucocorticoid levels is complex and often not easily interpretable in response to chronic stress. Moreover, it is important to note that while glucocorticoids are critically involved in the response to stressors and have historically received much attention in the research literature, there are a number of other mediators such as norepinephrine that mediate the stress response (Romero et al., 2009; Romero et al., 2015). We believe that the use of mathematical models will become increasingly important in resolving many of these challenges. Mathematical models can be used to study the emergent effects of complex interactions between multiple allostatic mediators as well as quantitatively understand individual variability in the regulation of physiological signaling, enabling the characterization of differences in allostatic load accumulation, and stress resilience. There is thus, a growing interest in developing mathematical models in order to encapsulate the concepts of allostasis and stress resilience within a more quantitative framework.

Much attention has been directed to the study of adaptive changes in allostatic brain circuits that occur during the development of addiction. In general, it is suggested that drug addiction involves anticipatory neuroadaptations that alter the neurobehavioral reward mechanisms in response to repeated substance use (George et al., 2012). Ahmed et al. developed a mathematical model for cocaine addiction dynamics, showing how a decrease in allostatic reward function due to the overactivation of compensatory brain antireward process could result in the increase in self-administration of the drug (Ahmed and Koob, 2005). By integrating pharmacokinetic, pharmacodynamic and motivational factors, the model was able to provide a quantitative framework for the progression of addiction.

Goldstein has proposed modeling interactions between physiological systems using elements from control engineering i.e. in terms of homeostats, interactions between multiple effectors, and homeostat resetting of set points (Goldstein, 2008). Using such a model, it was conceptually shown that the activation of effectors in response to a change in a monitored variable resulted in wear and tear, and decreased effector efficiency, analogous to physiological wear and tear upon activation of the stress response. Chronic activation could then lead to a substantial decrease in effector efficiency such that even continual activation of physiological effectors does not normalize the monitored variable. This approach has been extended to interconnected periodic systems to study the interaction between circadian disruption and allostatic load (Acevedo and Androulakis, 2017). The model results showed that the ability of the system to maintain a "homeostatic" entrained state depends on the phase relationships between homeostats, the frequency and the severity of stress exposure. More specifically, model results predicted that a synchronous periodic system is able to survive optimally, while asynchronous homeostats are not able to respond as well to chronic phase perturbations, resulting in an increased accumulation of allostatic load and an eventual breakdown of the oscillatory dynamics of the homeostats.

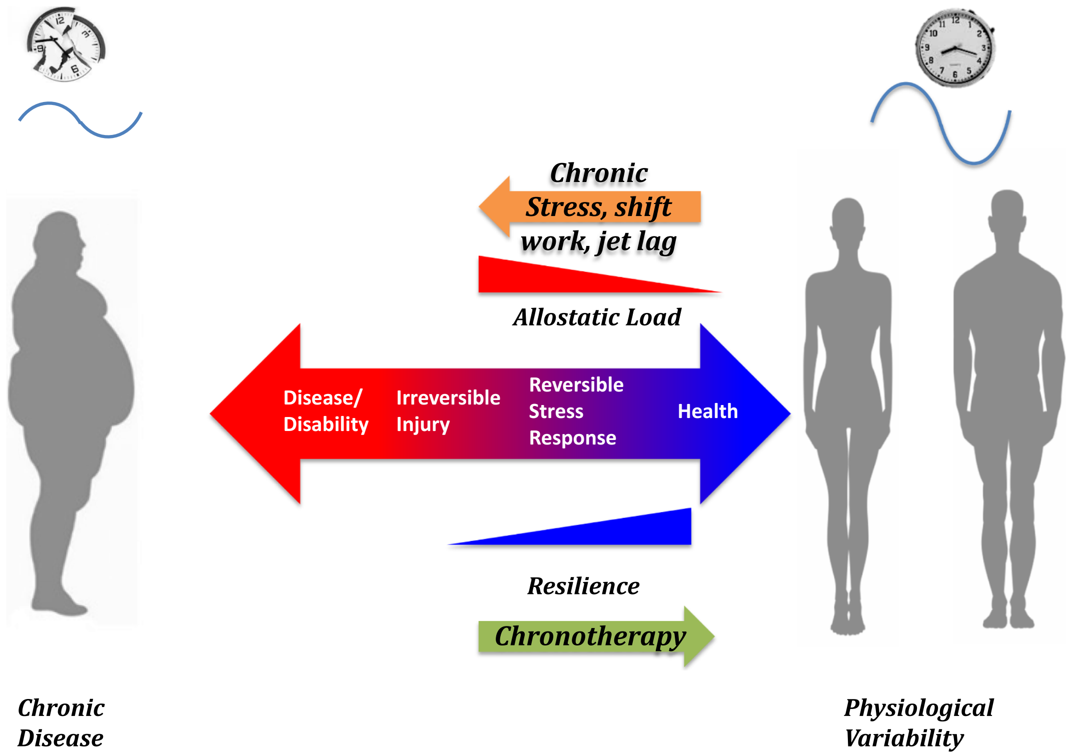

Fig. 2. The allostatic viewpoint provides an integrated view of host physiology emphasizing both the basal anticipatory nature of physiological mechanisms as well as the activation of adaptive processes in order to preserve homeostasis in response to stressors. An equal focus on both healthy and diseased states within the allostatic viewpoint further enables an improved characterization of physiological variability. Moreover, a careful consideration of the influence of circadian rhythms on allostatic mechanisms is critical for understanding the dynamics of physiological regulation. The chronic disruption of robust circadian dynamics results in the accumulation of allostatic load, a decrease in resilience to subsequent stressors and the development of chronic systemic diseases. Finally, we suggest that chronotherapeutic approaches can result in the re-engagement of allostatic adaptive mechanisms and the restoration of physiological stress resilience.

More recently, mathematical modeling has been used to study the influence of chronic stress habituation and individual variability in the circadian dynamics in response to chronic stress using biochemical models of the HPA axis. Model predictions suggest that allostatic habituation to chronic stress (i.e. return to pre-stress glucocorticoid levels) necessitates alterations in the feedforward and feedback mechanisms of the HPA network; specifically an increase in the feedforward adrenal sensitivity and the strength of negative feedback (Rao and Androulakis, 2017). Moreover, the model predicted that despite the ability of the system to return to pre-stress circadian rhythms upon allostatic habituation, the maximal response of the system to a subsequent acute stressor is sensitized, indicative of the accumulation of allostatic load. Interestingly, chronic stress sensitization upon allostatic habituation is frequently observed experimentally (Herman, 2013). Furthermore, simulated individuals with high pre-stress adrenal sensitivity were predicted to be more likely to exhibit chronic stress sensitization upon habituation. Finally, an individualized characterization of the regulatory dynamics of the HPA axis showed the existence of a trade-off between the two primary functions of the HPA axis; specifically, between its ability to be a robust circadian time-keeping mechanism and its ability to flexibly respond to acute stressors (Rao, 2018). As our quantitative understanding of allostatic mechanisms evolves, we believe that mathematical modeling will become an indispensable approach that yields not only a more precise characterization but also an improved conceptual foundation of physiological regulation.

7. Concluding remarks

In comparison to the framework of homeostasis, which is primarily focused on error-correction through negative feedback architectures, allostasis emphasizes not only adaptive responses involved in the preservation of critical physiological variables within a narrow homeostatic range but also the anticipation of regulatory needs based on a predictably varying environment. The focus on the anticipatory basal dynamics leads to a natural consideration of the circadian dynamics of the allostatic mediators, which influence their basal functioning, whereby they orchestrate the activation of diverse physiological signaling processes in a time-dependent manner as well as impact the stress-responsive behavior of these mediators. Thus, a primary goal of this review was to underscore the importance of the intricate interdependence between the circadian dynamics of critical physiological variables and the maintenance of homeostasis and stress resilience though the proper adaptive functioning of allostatic mechanisms. We suggest that the analysis of the circadian dynamics of physiological variables can thus, enable a high-level, integrated view of the regulation of host physiology.

The drastic changes in modern society have resulted in an environment that our physiological systems have not evolved to cope with. The chronic imposition of these “24/7” lifestyles causes the disruption of circadian rhythms, which we suggest results in a loss in the flexibility of adaptive allostatic mechanisms and compromises stress resilience.

Furthermore, using the concept of allostasis we can begin to understand how chronic stress and circadian disruption can eventually lead to the failure of allostatic adaptation and development of disease. Particularly, the emphasis on the basal anticipatory dynamics of regulatory systems such as the HPA axis provides a framework, which highlights the importance of studying not only the breakdown of allostatic mechanisms during chronic disease but also the importance of studying the regulation of physiological signaling in the healthy organism in equal measure (Romero et al., 2015) [Fig. 2]. By doing so, the allostatic viewpoint also lends itself to the consideration of both intra-individual and inter-individual variability through the analysis of life-histories, genetic and epigenetic differences. Finally, an improved understanding of the circadian dynamics of allostatic regulation can lead to the development of more nuanced "bottom-up" pharmacological approaches with fewer adverse effects, as well as improve the efficacy and reveal the mechanistic underpinnings of many "top-down" non-pharmacological and behavioral therapies for promoting physiological plasticity.

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Disclosure statement

The authors have nothing to declare.

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