REVIEW

The interplay between stress, circadian clocks, and energy metabolism

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Abstract

Endogenous circadian clocks adapt an organism's physiology and behavior to predictable changes in the environment as a consequence of the Earth's rotation around its axis. In mammals, circadian rhythms are the output of a ubiquitous network of cellular timers coordinated by a hypothalamic master pacemaker. Circadian clock function is closely connected to the stress response system which has evolved to ensure survival under less predictable situations of danger. Disruptions in both of these functions are highly prevalent in modern society and have been linked to pathologic alterations in metabolic setpoints, promoting overeating, obesity, and type-2 diabetes. This paper describes the different levels of interaction between the circadian clock and acute and chronic stress responses. It summarizes studies assessing clock-stress crosstalk in the context of metabolic homeostasis and outlines options to use this interaction for diagnostic and therapeutic measures targeting metabolic health and well-being in the highly chronodisruptive environment of modern 24-h globalized societies.

Key Words

- circadian clock
- energy metabolism
- stress
- chronic stress
- glucocorticoids

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Introduction

For most animals – and throughout most of evolution – this planet has been a very dangerous place. Nutrients were scarce and often difficult to find. At the same time, predators were roaming the same habitats. Only those individuals capable of utilizing sufficient amounts of energy to acquire food, avoid predation, and secure mating partners were able to transmit their genetic information to the next generation. Several regulatory systems have emerged during evolution that promote the availability of energy at times of need while minimizing overall energetic needs at other times. Two of these, the stress system and the circadian clock, work closely together for this goal, but use fundamentally different principles of activation. The stress response is a fast, demand activated program that is essential for survival in unpredictable danger situations (Ellis & Del Giudice 2019). In contrast, the circadian clock is a gradual, endogenously activated function that helps to anticipate predictable environmental changes brought about by the Earth's rotation around its axis, and thus, the 24-h succession of day and night (Pittendrigh 1993).

Besides their impact on various other aspects of physiology, both systems converge on the regulation of energy metabolism (Ramsey *et al.* 2007, Ford *et al.* 2017). In our modern societies, both are subject to frequent deregulation, be it from complex social interactions and environmental demands in the case of the stress system or nocturnal light pollution and sleep-wake rhythm disruption in the case of the circadian clock. Ultimately, these perturbations synergize in their disruption of metabolism and energy homeostasis, arguably among the key medical challenges of the twenty-first century (Herold *et al.* 2015).

This short review summarizes the main regulators of stress and clock systems in mammals with a focus on their

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mutual interaction in the regulation of energy metabolism. It highlights the detrimental effects of modern lifestyles on this interaction and suggests approaches to stabilize stress-clock-metabolism balance as a fundamental aspect of physiologic and psychologic well-being.

Evolutionary aspects of stress systems

In an acutely dangerous situation, our body needs to rapidly mobilize danger response systems to evade the risk of injury or even death. Sensory perception is increased, energy equivalents are mobilized and oxygen supplies to nervous and muscle tissues are upregulated. In consequence, stress promotes the accelerated depletion of energy stores due to an increase in energy expenditure. Ideally, such transient boost of energy turnover enables the organism to quickly evaluate the potential danger and initiate an appropriate *fight-or-flight* response. After the resolution of the situation and the neutralization of the challenge or danger, the stress system returns to baseline levels allowing for rest, regeneration, and the replenishment of energy stores (Russell & Lightman 2019).

At the physiological level, the stress response comprises two different components (Tsigos *et al.* 2000). The first involves central and systemic autonomic activation and the release of catecholamines – adrenaline and, to a lesser extent, noradrenaline – from the adrenal medulla (Wong 2006). This fast/acute response is trailed by an activation of the multi-step hypothalamus–pituitary–adrenal (HPA) axis and the release of glucocorticoids (GCs) – cortisol in humans and other primates, corticosterone in rodents – with a delay of several minutes (Kirschbaum *et al.* 1993). Consequently, also the downstream effects of these two endocrine stress effector systems show very different temporal kinetics. Catecholamines are highly soluble molecules that are stored in vesicles in the adrenergic medulla. Upon stress, these vesicles fuse with the plasma membrane and simultaneously release large amounts of molecules into the bloodstream (Douglas & Rubin 1961). Once reaching their target tissues, catecholamines signal through activation of G-protein-coupled plasma membrane receptors and rapid second messenger-mediated signal transduction. GCs, on the other hand, are highly lipophilic. HPA axis activation promotes *de novo* synthesis of GCs from cholesterol. These then enter the bloodstream *via* diffusion through the mitochondrial and plasma membranes of adrenocortical cells (Turcu & Auchus 2015). In the blood, GCs – because of their lipophilic nature – need to be transported by specific transporter proteins such as transcortin and albumin. At target tissues, GCs pass the plasma membrane to bind type-1 nuclear receptors that, after dimerization and nuclear translocation, act as transcription factors to affect cellular physiology through alterations in the enzymatic repertoire (Timmermans *et al.* 2019). This GC-mediated response takes minutes to hours to complete, making it less suited for fight-or-flight responses, but rather for intermediate-term adaptations to a stressful environment.

Both response systems share several targets, but while the autonomic/catecholaminergic response primarily affects the sensory and cardiovascular system, the endocrine axis/GC response mainly promotes the redistribution of energy equivalents while at the same time suppressing digestive and immune functions, two other biological systems of high energy demand (Tsigos *et al.* 2000).

When the organism experiences repeated or long-lasting stressful situations, regulation of the stress system is chronically altered (McEwen 2017). During evolution, such extended stress situations were confined to unique events such as pregnancy or extreme environmental conditions. The complex demands of modern societies, however, have changed this situation fundamentally. The stress system adapts to ongoing psychosocial stimulation by rebalancing its two effector functions, promoting constant low-level activation of the autonomic system and a rebalancing of the negative feedback system controlling HPA axis function (McEwen 2017). Excitatory amino acids such as glutamate have a key function in the central adaptation to chronic stress. Excess glutamate release during chronic restraint stress in rodents leads to shrinkage of apical dendrites in neurons of the hippocampus (McEwen 2016) and the prefrontal cortex (Martin & Wellman 2011) – two sites that also show robust functional circadian regulation (Chen *et al.* 2016, Snider *et al.* 2018). Activation of autonomic networks (Thome *et al.* 2017) and the sympathetic outflow from the brain is an important mediator of acute and chronic stress-induced disorders such as hypertension, obesity, and heart disease (Hering *et al.* 2015). Repeated exposure to the same stressor can result in habituation of HPA axis function, for example, decreasing GC responses over time, which requires active mineralocorticoid receptor (MR) signaling (Cole *et al.* 2000). Chronic exposure to stressors that involve non-social interventions (e.g. repeated immobilization or footshocks) leads to an upregulation of *Crh* mRNA expression in the PVN (Imaki *et al.* 1991, Mamalaki *et al.* 1992, Herman *et al.* 1995, Figueiredo *et al.* 2003). In parallel, chronic variable stress reduces

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GR in this area (Herman *et al.* 1995, Makino *et al.* 1995). Together, these two effects blunt the negative feedback of GCs on HPA axis regulation underlying elevated baseline GC concentrations characteristic for chronic stress adaptation. In consequence, chronic stress exposure increases tonic, but at the same time decreases phasic GC output from the HPA axis. On the long run, cardiovascular function, metabolic homeostasis, and central mood and motivation systems suffer from this, increasing the risk of developing chronic diseases such as arteriosclerosis, obesity, and major depression, respectively (Huang *et al.* 2013).

Stress and metabolism – acute vs chronic effects

Stress signals elevated energy demands to the body. From this perspective, the first-glance contradictory effects of acute and chronic stress on the regulation energy homeostasis start to make sense. In an acute stress situation, the body needs fast energy to fuel sensory perception, cognitive processing, and muscle activity in the fight-or-flight response. Taking in additional energy in the form of food would rather distract from this task and, hence, appetite and digestive metabolic functions are suppressed (Fig. 1). This changes under chronic stress conditions. While the body continues to fuel additional energy into cognitive and muscle systems, it also ensures that the body's energy supply lines do not run dry by increasing appetite and promoting the capacity of energy stores such as the liver and adipose tissues to refill or even increase their capacities (McEwen 2017). Important factors in this response are GCs and the appetite-promoting stomach-secreted peptide ghrelin. Elevated central GCs increase expression of the orexigenic hypothalamic neuropeptide NPY *via* inhibition of CRH (Zakrzewska *et al.* 1999). NPY also decreases anxiety and has been implicated in emotional eating (Kim *et al.* 2003, Yehuda *et al.* 2006). Activation of the HPA axis further upregulates the central release of endogenous opioids (O'Hare *et al.* 2004). Opioids decrease activity of the HPA axis, thus attenuating over-shooting stress responses (Kreek & Koob 1998). At the same time, they increase palatable food intake and *vice versa*. If stress becomes chronic and eating becomes associated with stress coping, highly palatable food may become addictive (Volkow *et al.* 2017). Exposure to chronic social defeat results in elevated plasma concentrations of ghrelin that remain high long after the end of the stress intervention itself. In the pituitary, ghrelin further amplifies the activity of the HPA axis (Spencer *et al.* 2012). In the brain, ghrelin acts on various sites to attenuate anxiety and depressive-like behaviors (Lutter *et al.* 2008, Spencer *et al.* 2012). It also potently increases appetite through activation of orexigenic neurons in the mediobasal hypothalamus (Nakazato *et al.* 2001, Wren *et al.* 2001).

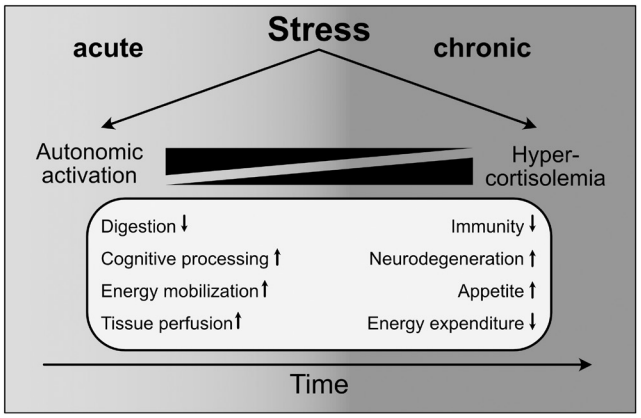

Figure 1
Physiological responses to acute and chronic stress. During acute stress, autonomic effects aim at mobilizing energy resources to enable the fight-or-flight response and evade imminent danger. Under repeated or chronic stress exposure endocrine, glucocorticoid-mediated effects become more dominant regulating energy supplementation under extended elevated energetic needs. In consequence, extended stress may lead to pathology-promoting neuronal, immune and metabolic adaptations.

In a more natural environment, in which it may take a certain effort to ensure energy supplies, these changes in the regulation of energy utilization enable the body to survive through extended stress periods. Metabolic setpoints, that is, regulatory 'references' that enable the system to approximate a physiological state of homeostasis. In our modern society, however, we have no problems refilling our energy stores and the stimulation of appetite during extended stress easily overshoots physiological demands, promoting weight gain and adiposity (Razzoli *et al.* 2017). Moreover, unlike our ancestors, modern society often puts us under stressful psychological situations for months and years, for example, in competition for social and professional recognition, which has been shown to add an additional level of stress-related wear out (Cohen *et al.* 2007).

The perception of stress is influenced by experiences and genetics. When the brain perceives stress over extended time spans, physiological and behavioral responses are initiated leading to allostasis, that is, a shift in homeostatic setpoints, and adaptation. Over time, such allostatic load can accumulate and have adverse

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effects on various organ systems, leading to disease (Suvarna *et al.* 2020). In the CNS, chronic stress promotes the development of depression and neurodegenerative processes (Swaab *et al.* 2005). In the periphery, chronic stress adaptations cause obesity, cardiovascular complications, and impaired immune responses (Steptoe & Kivimäki 2012, Dumbell *et al.* 2016, Razzoli *et al.* 2017). It is difficult to say to which extent these effects may have an evolutionary explanation or simply reflect exhaustion of an overwhelmed stress coping system under unnatural conditions.

The main agents in the long-term metabolic effects of chronic stress are GCs acting through binding to, both, glucocorticoid (GR) and mineralocorticoid nuclear receptors (MR) and eliciting transcriptional adaptive programs in peripheral tissues and the CNS (Reul & de Kloet 1985). Chronic stress is a major risk factor for obesity and metabolic diseases. However, the relationship between stress hormones and energy metabolism is complex. For example, while some people increase food intake and body weight during stress, others show the opposite phenotype with reduced eating and weight loss (Harris 2015). Moreover, stress-induced hyperphagy is not necessarily followed by an increase in adiposity and body mass, suggesting that mechanisms to regulate energy consumption are activated at the same time (Dallman *et al.* 2003). In part, this may be explained by conflicting responses of the autonomic and the endocrine axis stress mediator systems. GCs boost energy consumption and inhibit energy expenditure to promote a positive energy balance. In contrast, sympathetically activated beta-adrenergic receptors increase energy expenditure by activating thermogenesis in brown adipose tissue (BAT) to favor a negative energy balance – a process that is suppressed by GCs (Hardwick *et al.* 1989). Therefore, stress may promote weight gain only if hyperphagy prevails (Dallman *et al.* 2003). In the presence of stress-induced hypophagy – or if BAT recruitment dominates – weight loss will result. Despite these clear effects of stress on metabolic regulation, only few molecular mediators at the interface between stress and metabolic regulation have been discovered. Importantly, circadian clocks may play an important role in this interaction.

The circadian clock system

Circadian clocks have evolved to anticipate recurring changes in environmental conditions brought about by the Earth's rotation around its axis. In mammals, molecular clocks are found in all tissues and cells of the body. They are coordinated by a master clock residing in the hypothalamic suprachiasmatic nucleus (SCN) (Reppert & Weaver 2002). The SCN receives projections from intrinsically photosensitive ganglion cells expressing the blue-light sensitive photopigment melanopsin (OPN4). Through these projections, SCN neuronal firing rhythms are synchronized with the external light–darkness cycle (Lucas *et al.* 2012). Coordination of clock function in non-SCN central and peripheral tissues occurs through multiple pathways including endocrine, autonomic and behavioral outputs (Astiz *et al.* 2019). Of note, GCs have been implicated in this systemic coordination of circadian clock function. Treatment with GR agonists can reset clocks *in vitro* and *in vivo*, while genetic or pharmacologic alteration of GR signaling affects clock network resetting after phase-shifting stimuli (Balsalobre *et al.* 2000, Kiessling *et al.* 2010). In their potential to affect clock function in different tissues, GCs are very similar to another endocrine clock factor, melatonin (Pfeffer *et al.* 2018). Interestingly though, neither the loss of melatonin nor GC function markedly interferes with circadian clock network organization in mice, suggesting highly redundant means of systems coordination in the mammalian clock system (Astiz *et al.* 2019).

At the molecular level, circadian clocks are comprised of interlocked transcriptional–translational feedback loops (TTLs) involving a set of clock genes and proteins (Takahashi 2017). In the mammalian core TTL, the transcription factor dimer circadian locomotor output cycles kaput (CLOCK, which may in some tissues be replaced by neuronal PAS protein 2 – NPAS2)/brain and muscle ANRT-like 1 (BMAL1/ARNTL) activates expression of three period (*Per1–3*) and two cryptochrome genes (*Cry1/2*) during the day. PER and CRY proteins dimerize and, toward the end of the day, translocate into the nucleus where they inhibit CLOCK/BMAL1, thus shutting down their own transcription. Toward the end of the night, PER and CRY proteins are degraded resulting in a disinhibition of CLOCK/BMAL1 transactivation and a new molecular circadian cycle. The period of this TTL is modulated by several post-translational modifiers and by additional feedback loops involving further transcription factors such as albumin D-site binding protein (DBP) and reverse erythroblastoma alpha/beta (REV-ERBa/b, aka NR1D1/2) that affect abundance, localization, and turnover of the main TTL components (Buhr & Takahashi 2013, Takahashi 2017).

The rhythm in clock gene transcription is translated into physiologically meaningful signals through

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tissue-specific transcriptional programs *via* circadian promoter elements such as enhancer (E-) boxes, albumin D site (D-) boxes and *RORE*s (retinoic acid-related orphan receptor response elements) (Ukai & Ueda 2010) (Fig. 2). It is estimated that between 5 and 10% of protein-coding genes in a given tissue – 40–50% across the whole body – are expressed with a circadian rhythm (Zhang *et al.* 2014). Of note, just like the delayed-action GC-mediated stress response, circadian clock regulation acts through slow, transcription/translation-dependent alterations of the cellular enzymatic setup. Thus, just like GCs, the clock system is poorly equipped to respond to rapid changes in the environment, but rather serves to adapt the body to gradual or predictable alterations in demands.

Clocks and metabolism

Circadian clocks and energy metabolism are mutually linked to each other. Circadian disruption – either genetically or through external perturbations such as shift work, sleep curtailment, or nocturnal light pollution – is an independent risk factor for the development of metabolic disorders, from obesity and type-2 diabetes to cardiovascular complications and even cancer (Levi & Schibler 2007, Ramsey *et al.* 2007). Sleep curtailment has been shown to rapidly reduce insulin sensitivity and affect appetite and high-energy food craving in laboratory studies (Reutrakul & Van Cauter 2018). Animal experiments show that circadian clocks are important regulators of glucose and lipid handling and storage. For example, pancreatic b-cell clocks control insulin secretion, while adipose tissue clocks regulate lipolytic triglyceride breakdown and fatty acid release which, in turn, affects central circuits of appetite regulation (Paschos *et al.* 2012, Shostak *et al.* 2013, Perelis *et al.* 2015) (Fig. 3).

At the cellular level, circadian clocks are involved in the regulation of mitochondrial function and, hence, ATP production. Important enzymes of carbohydrate and lipid metabolism such as phosphenol pyruvate carboxykinase (PEPCK), apolipoprotein A4 (APOA4), and fatty acid synthase (FAS), among many others, are direct transcriptional targets of the circadian clock machinery (Zhang *et al.* 2014). As one example, in mouse liver, 16 % of all protein-coding genes were found to be rhythmically expressed, though only a fraction of these seem to be directly regulated by the local clock machinery (Zhang *et al.* 2014, Greenwell *et al.* 2019). Others respond rather to systemic rhythmic factors such as hormones, feeding-related signals or body temperature (Harder & Oster 2020). This complex interaction of external and local signal in the temporal regulation of the metabolic

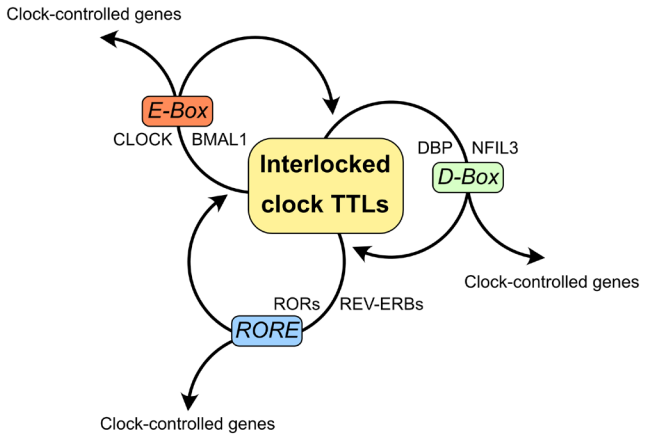

Figure 2
Coordination of cellular physiology through clock-controlled genes. The interlocked system of transcriptional–translational feedback loops (TTLs) comprising the cellular circadian clock regulates cellular function through the coordination of tissue-specific transcriptional programs and circadian promoter elements such as *E-boxes*, *D-boxes* and *RORE*s. *E-boxes* are activated by the clock proteins CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle ANRT-like 1); *D-boxes* by DBP (albumin D-site binding protein) and NFIL3 (nuclear factor, interleukin 3 regulated); and *RORE*s by ROR (retinoid orphan receptor) and REV-ERB (reverse erythroblastoma) proteins. The combination of these circadian regulatory elements in the promoters of clock-controlled genes defines their phase of expression.

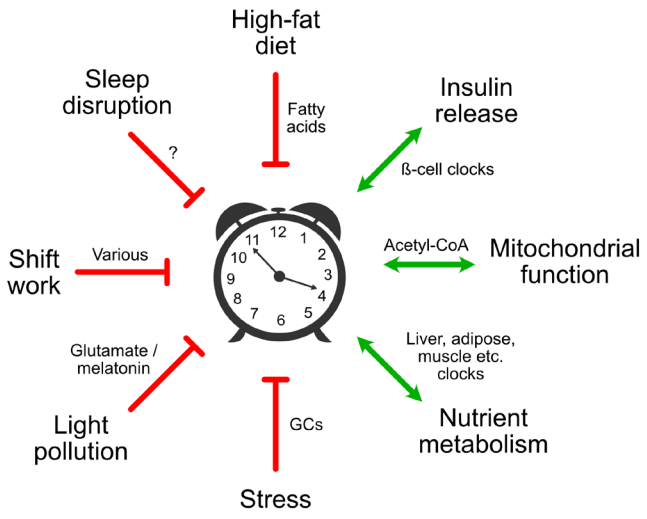

Figure 3
Chronodisruption alters energy metabolism. Several typical conditions of our modern 24-h society are capable of disrupting circadian rhythms through interaction with central and peripheral tissue clocks. These effects are mediated by endocrine factors such as glucocorticoids (GCs) or melatonin, but also through metabolites and neuronal activity. The circadian clock system and energy metabolism influence each other through rhythmic coordination of metabolic factors and cellular metabolism. For more details see the 'Clocks and metabolism' section.

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machinery suggests two things: metabolic tissue functions adapt to acute external demands but, at the same time, are subject to temporal modulation by the endogenous timing system. The clock ensures baseline adaptation to recurring and, thus, predictable changes in metabolic demands along the day while also temporally modulating – or gating – responsiveness of the system to external stimuli. At the same time, the system remains principally sensitive to less predictable changes. In line with this, external perturbation of circadian regulation often has more profound effects on metabolic homeostasis than genetic dysfunction of the local clock machinery (Meyer-Kovac *et al.* 2017, Heyde & Oster 2020).

Interestingly, changes in metabolic state can feedback on clock function at several levels, thus altering tissue gene expression programs, but also circadian rhythms of behavior such as sleep or food intake. Switching mice from a standard low-fat chow to a Western style high-fat diet disrupts diurnal food intake profiles and rhythms of gene expression in several tissues and even slows down the SCN pacemaker (Kohsaka *et al.* 2007). This crosstalk has important implications for real-life situations of chronodisruption, for example, in shift workers. Behavioral intervention studies in rodents and humans have shown, for example, that stabilizing circadian feeding/fasting rhythms may have substantial metabolic benefits under obesogenic conditions (Chaix *et al.* 2014, Gill & Panda 2015, Meyer-Kovac *et al.* 2017). Transgenic mouse studies suggest that the effects of, for example, time restricted feeding patterns on general well-being and health may even overcome genetic disruptions of the core clock machinery (Chaix *et al.* 2019).

At the cellular level, changes in metabolic state can directly affect the function of the circadian TTL. REV-ERBs are ligands for the metabolic sensor heme, and the capacity of CLOCK(NPAS2)/BMAL1 dimers to bind DNA and activate transcription depends strongly on the cellular redox state (Rutter *et al.* 2001, Yin *et al.* 2007). In this way, acute oxidative changes upon food intake may reset molecular clock gene rhythms and downstream cellular metabolic processes. Interestingly, the timing of food intake has strong effects on clock function in peripheral tissues. In extreme situations such as repeated rest phase feeding this may lead to a complete uncoupling of the peripheral clock machinery from the SCN pacemaker that stays locked to the external light–darkness cycle (Damiola *et al.* 2000). Such state of internal desynchrony would result in a temporal mismatch of appetite regulatory circuits and metabolic tissue networks which, under modern conditions of easy food access, alters metabolic setpoints promoting hyperphagy and obesity. Indeed, work in rodents has shown that restoring circadian network coordination positively affects energy homeostasis under obesogenic conditions (West *et al.* 2017, Kolbe *et al.* 2019).

Clocks and stress

The mechanisms of systemic circadian entrainment are still poorly understood. As outlined previously, we know that the SCN uses both humoral and neural pathways to transmit time information across the clock network (Astiz *et al.* 2019). Among the best studied humoral mediators of circadian entrainment are GCs. Under non-stressed conditions, circulating GC levels show robust diurnal rhythmicity peaking at the beginning of the active phase (i.e. in the morning in diurnal humans and in the evening in nocturnal rodents). Circadian GC rhythms are involved in the coordination of clock function in central and peripheral tissues (Oster *et al.* 2016). The circadian control of GC secretion results from an interaction between the SCN and tissue clocks along the HPA axis (Leliavski *et al.* 2015) (Fig. 4). The SCN controls the rhythmic secretion of the adrenocorticotropic hormone (ACTH) from the pituitary gland *via* regulating the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)

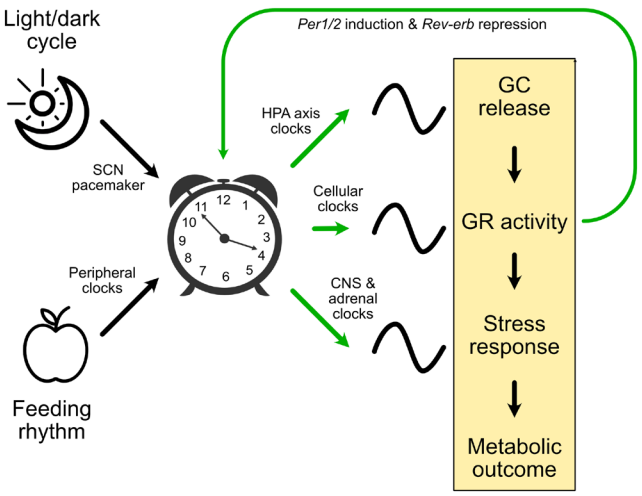

Figure 4
Circadian gating of the stress response. Circadian clocks are synchronized by external zeitgebers such as light (*via* the SCN pacemaker) or food (*via* peripheral tissue clocks). The circadian clock network affects stress responses at the level of GC baseline release, GR abundance and activity, and acute stress responses, for example, by regulating the sensitivity of the adrenal steroidogenic machinery to ACTH stimulation. Importantly, stress can also feedback on clock function through GC/GR-mediated regulation of clock gene transcription.

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from the paraventricular nucleus of the hypothalamus (PVN). ACTH, in turn, promotes GC biosynthesis and release from *zona fasciculata* cells of the adrenal cortex. Through the autonomic nervous system, the SCN at the same time synchronizes adrenal cellular clocks to regulate the time-of-day dependent sensitivity of the adrenal steroidogenic machinery to ACTH stimulation (Oster *et al.* 2006). Phase coherence of these two principle arms of the stress axis circadian system is required for high-amplitude rhythmic secretion of GCs.

Coupling between the stress system and the circadian clock is similarly observed at the molecular level. Due to its high affinity for GCs, MR is constitutively activated under most physiological conditions (Reul & de Kloet 1985). In contrast, GRs are only activated at higher GC concentrations that cause phasic reactions, that is, at the circadian peak or in acute stressful situations (de Kloet *et al.* 2005). Upon ligand binding, GR dimers translocate from the cytosol into the nucleus, where they bind to glucocorticoid-responsive element (*GRE*) motifs in regulatory regions of target genes, including several core clock genes such as *Per1/2* (So *et al.* 2009, Reddy *et al.* 2012). In contrast, the *Rev-erbα* locus contains negative *GRE*s that mediate GR trans-repression (Torra *et al.* 2000). Recent studies suggest that clock proteins and GR can also interact at the protein level. CLOCK has acetyl transferase activity and is capable of acetylating GR to reduce its DNA-binding capacity (Nader *et al.* 2009). CRY proteins bind GR directly (Lamia *et al.* 2011). Finally, the presence of REV-ERBα affects the nuclear translocation of GR upon GC binding through interaction with heat shock proteins (Okabe *et al.* 2016).

In the adrenal glands, GCs and clock genes further interact in the modulation of catecholamine biosynthesis and breakdown, thus strengthening the coupling between the circadian and the stress system. Transcription of the catecholamine breakdown enzyme monoamine oxidase I (MAOA) is a direct target of CLOCK/BMAL1 (Hampp *et al.* 2008). On the other hand, expression of the pacemaker enzyme of catecholamine biosynthesis, tyrosine hydroxylase (TH), is suppressed by REV-ERBα (Jager *et al.* 2014; but also see Lemos *et al.* 2007). GR regulates the expression of catechol-O-methyltransferase (COMT) involved in catecholamine catabolism (Lindley *et al.* 2005). In summary, interactions between GCs/GR and the clock machinery may affect both fast- and delayed-response/chronic stress systems.

Classic animal studies suggest that the extent of a specific stress response strongly depends on the time of day (Zimmermann & Critchlow 1967, Gibbs 1970, Dunn *et al.* 1972, Gallant & Brownie 1979). During the active phase, physical stressor exposure like hemorrhage (Lilly *et al.* 2000), hypoglycemia (Kalsbeek *et al.* 2003), or oxidative stress (Antoch *et al.* 2005, Fanjul-Moles & López-Riquelme 2016) results in a greater increase in circulating GCs than at other periods of the day. In contrast, during the inactive phase, restraint/immobilization, foot shock, or shaking stress results in a stronger increase in GC and ACTH release and in blood pressure (Bradbury *et al.* 1991, Gattermann & Weinandy 1996, Mathias *et al.* 2000, Bernatova *et al.* 2002, Retana-Márquez *et al.* 2003, Gutiérrez-Mariscal *et al.* 2012). More experiments are needed to clarify how exactly time-of-day affects the responsiveness to stress. Similarly, there is evidence for a time-of-day dependent adaptive response to repeated or chronic stress. Along this line, genetic disruption of the circadian clock system in mice dramatically changes the baseline activity and responsiveness of the stress system. Mice lacking either BMAL1 or CLOCK show hypocortisolism and acute stress resistance at behavioral and hormonal levels (Turek *et al.* 2005, Leliavski *et al.* 2014). Less conclusively, for mice lacking specific genes of the negative branch of the circadian TTL both hyper- and hypocortisolism have been reported (Dallmann *et al.* 2006, Lamia *et al.* 2011, Barclay *et al.* 2013). Of interest in the context of energy metabolism, stress responses are exaggerated under high-fat diet conditions – but only at certain times of the day (Appiakannan *et al.* 2019).

Chronodisruption, chronic stress and metabolic consequences

Chronodisruption, that is, the alteration of behavioral and physiological rhythms relative to the natural 24-h day cycle, is a common phenomenon in modern societies. The invention of electric lighting has paved the way into industrialism and the uncoupling of activity schedules from the natural light–darkness cycle. Shift work is increasingly prevalent with 20–30% of the total workforce operating under non-standard or rotating shift conditions in European, North American and East Asian countries (Brown *et al.* 2020). Another chronodisruptive factor is the internationalization of markets with increased trans-meridian travel and communication.

As mentioned earlier, both chronodisruption and stress may have independent as well as interactive effects on energy metabolism. Chronodisruptive conditions such as shiftwork are perceived as psychological stressors *per se* (Faraut *et al.* 2013). In consequence, relative to

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non-shift workers, shift workers have a higher risk for numerous adverse stress-associated health outcomes such as cardiovascular and gastrointestinal disorders, obesity, and some types of cancer (Kecklund & Axelsson 2016). Even more related to stress, individuals working in shifts suffer more from psychiatric disorders such as depression, anxiety, and alcohol abuse (Walker *et al.* 2020). Finally – and again very similar to chronic stress effects – shift work negatively impacts on neurocognitive performance (Devore *et al.* 2013). In modern work environments, chronodisruption and psychosocial stress are often so intricately entwined that it is rather difficult to dissociate stress-specific from chronodisruptive aspects of metabolic and other disorders in the clinics. The immune system as another shared target of both stress and clock programs may play an important role in this crosstalk. Dampened cortisol rhythms and weakened stress responses have been observed in patients with immune diseases such as bronchial asthma, allergic rhinitis, or sepsis (Fei *et al.* 2004, Lesur *et al.* 2010, Fidan *et al.* 2013). *Vice versa*, early-life exposure to endotoxin reprograms the HPA axis in rats, leading to GC hypersensitivity (Shanks *et al.* 1995).

Chronic stress has significant adverse effects in humans and – under conditions of easy access to high-calorie food – promotes hyperphagy and the development of obesity and type-2 diabetes (Adam & Epel 2007). Even under physiological conditions, GCs have anabolic functions in the liver, stimulating gluconeogenesis and glycogen storage. GCs also inhibit glucose utilization in many peripheral tissues. Together, this leads to an increase in blood glucose levels and stimulates insulin secretion (Oster *et al.* 2016). In consequence, transient GC boosts during acute stress episodes efficiently suppress appetite and may even lead to weight loss (Razzoli *et al.* 2017). In contrast, chronic stress increases appetite for high-calorie foods and hyperglycemia (Dallman *et al.* 2003). In addition, chronic stress-associated GC changes may decrease insulin sensitivity in many tissues, thus promoting the development of type-2 diabetes (Joseph & Golden 2017). Finally, GC resistance is associated with reduced GR expression in adipose tissue and increased triglyceride storage due to suppressed lipolysis (Shen *et al.* 2017).

Considering this interaction, studies on social stress associated with circadian rhythm disorders are of great clinical interest. Repeated (non-social) experimental stress is more detrimental to rats when applied during the rest phase, that is, the day. Chronic mild stress promotes depressive and anxiety-related behaviors when used during the day, but not at night (Aslani *et al.* 2014). Stress induced by exposure to cat odor, immobilization stress or tail shocks also has more detrimental effects when applied repeatedly during the inactive phase (Retana-Márquez *et al.* 2003, Cohen *et al.* 2015, Fonken *et al.* 2016).

A common mouse model for social stress with good translational relevance is the social defeat (also known as the resident intruder) paradigm, in which the experimental animal (the intruder) is placed for a short time in the home cage of a superior resident. Within seconds to minutes, this usually leads to submission with physical and social stress mimicking social conflicts in humans. Interestingly, most social defeat studies indicate a more harmful effect of nighttime stress, but metabolic effects are predominantly observed in response to stress during the inactive phase (Rybkin *et al.* 1997, Bartlang *et al.* 2012, 2014, 2015). In rats, stress during the active phase does not affect body weight, which indicates a circadian regulation of chronic/repeated stress responses (Gorka & Adamik 1993). Adjustments to repeated social defeat stress in mice, on the other hand, occur more frequently during the active phase (Koch *et al.* 2016). Specifically, 19 days of social daytime stress in mice led to a transient reduction in bodyweight, but no alterations in HPA axis activity at the predicted time of social stressor exposure. In contrast, repeated nighttime stressor exposure led to alterations in food metabolization and reduced HPA axis activity with lower hormone concentrations at the time of predicted stressor exposure (Koch *et al.* 2016). Together, these data suggest a circadian gating of stress adaptation to predictable social defeat stress at the level of the HPA axis with impact on metabolic homeostasis.

Of note, most stress studies in rodents are done during normal laboratory hours, which is the inactive phase of nocturnal rodents. The inherent complexity of social stress paradigms and poor control for circadian effects may explain why results from different stress studies frequently yield contradictory results. We clearly need more time-controlled studies in humans to translate these findings into real-life recommendations and treatments.

Conclusions

Chronodisruption and psychosocial stress are hallmarks of modern societies. Both share common signaling components, most notably GCs, and – under chronic conditions – have very similar pathophysiological consequences such as immunosuppression and disruption of metabolic homeostasis. Assessing circadian

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clock function in the context of acute and chronic stress may yield important insight into the physiological underpinnings of this psychological concept. Considering the detrimental consequences of chronic stress exposure on metabolic – but also neurologic – function and well-being, the circadian system may provide promising inroads into improving established and developing new treatments for some of the most prevalent chronic pathologies of our modern societies such as major depression, obesity, and type-2 diabetes. As a start, circadian time needs to be recognized as a potential confounder in stress studies and the clinics. On the other hand, alterations in the circadian timing system may serve as biomarkers of stress impact and as predictors of pathological outcome. Along the same line, interventions aimed at restoring normal circadian function such as light therapies, interval fasting, or pharmacological interventions may, through clock-mediated impact on stress responses and metabolism, counteract the detrimental effects of stress at several levels. Finally, timing of unavoidable stressful events to specific times of the day may help with stress coping and improve well-being and performance, for example, at the workplace.

Declaration of interest

H O has received presentation honoraria from AbbVie, Shire Pharma, and Novo Nordisk. H O holds a patent on GC manipulation circadian synchronization (US Patent # 9,770,444).

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Author contribution statement

H O wrote the paper.

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