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Interaction between circadian rhythms and stress

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ABSTRACT

Life on earth has adapted to the day-night cycle by evolution of internal, so-called *circadian* clocks that adjust behavior and physiology to the recurring changes in environmental conditions. In mammals, a master pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus receives environmental light information and synchronizes peripheral tissues and central non-SCN clocks to geophysical time. Regulatory systems such as the hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), both being important for the regulation of stress responses, receive strong circadian input. In this review, we summarize the interaction of circadian and stress systems and the resulting physiological and pathophysiological consequences. Finally, we critically discuss the relevance of rodent stress studies for humans, addressing complications of translational approaches and offering strategies to optimize animal studies from a chronobiological perspective.

Contents

1. The molecular clock

The ability to anticipate daily changes in the environment conveys an evolutionary advantage to most species on earth. Therefore, organisms ranging from plants to higher mammals have developed endogenous circadian clocks that allow them to estimate the time of day. In the absence of external time cues these clocks free-run with a period close to 24 h. In order to compensate

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discrepancies between this intrinsic period and the environmental cycle, circadian clocks entrain to external *Zeitgebers* (from German *time giver*), with light being the most potent one. Unlike most biochemical systems, the period of the circadian clock is temperature compensated, a feature that is especially important for poikilothermic species (Buhr and Takahashi, 2013).

In mammals, the circadian clock is based on a molecular oscillator present in virtually every cell of the body. It is built from transcriptional-translational feedback loops (TTLs) generating self-sustained oscillations even on the cellular level. The clock's core TTL is composed of the genes *brain and muscle arnt-like 1* (*Bmal1*), *circadian locomotor output cycles kaput* (*Clock*), *cryptochrome* (*Cry*) *1/2* and *period* (*Per*) *1–3*. BMAL1 and CLOCK proteins form the positive limb of this core TTL. They belong to the family of basic helix-loop-helix transcription factors and act as heterodimers binding to *E-box* regulatory elements within the promoters of *Cry* and *Per* genes (Fustin et al., 2009; Gekakis et al., 1998; Hogenesch et al., 1998; Yoo et al., 2004), activating transcription of *Per* and *Cry*. PER and CRY proteins constitute the negative feedback limb of the circadian core TTL. Over the course of the day they accumulate in the cytoplasm and form complexes that translocate back into the nucleus where they inhibit BMAL1/CLOCK-mediated transcription (Kume et al., 1999; Zheng et al., 2001). Before the next cycle can start, the BMAL1/CLOCK heterodimer has to be reactivated. This is achieved by proteasomal degradation of the PER and CRY repressor complex. PER1 and PER2 are subject to phosphorylation mediated by casein kinases 1 delta and epsilon. This phosphorylation mark leads to their ubiquitination and subsequent degradation by the ubiquitin proteasome system (Camacho et al., 2001; Eide et al., 2005). Similarly, adenosine monophosphate-activated protein kinase (AMPK) and glycogen synthase kinase 3 beta (GSK3β) phosphorylate CRY1 and CRY2, respectively (Harada et al., 2005; Lamia et al., 2009), so that they are ubiquitinated and degraded. Decreasing levels of CRY and PER terminate the repression of BMAL1/CLOCK-mediated transcriptional activation so that the clock can move to the next cycle.

Besides this core loop, there are accessory feedback loops and additional levels of regulation to stabilize the molecular oscillations and mediate additional fine-tuning. The most prominent accessory TTL consists of *reverse erythroblastoma* (*Rev-Erbα/β*) and *retinoic acid receptor-related orphan receptor* (*RORα-γ*) that also contain *E-boxes* within their promoter regions. The BMAL1/CLOCK heterodimer binds to these *E-boxes* and activates transcription of *Rev-Erbs* and *RORs* (Buhr and Takahashi, 2013). In turn, REV-ERB proteins exert a negative feedback, inhibiting *Bmal1* transcription (Liu et al., 2008; Triqueneaux et al., 2004). RORs, in contrast, are positive regulators of *Bmal1* transcription and compete with REV-ERBs for *retinoid orphan receptor response element* (*RORE*) binding sites within the *Bmal1* promoter (Akashi and Takumi, 2005). REV-ERBα and β are functionally redundant and are considered to be essential for *Bmal1* oscillation. RORs seem to have a modulatory function, but they are dispensable for rhythmic transcription of *Bmal1* per se (Liu et al., 2008).

This molecular clock machinery is present in all nucleus-containing cells of an organism. In order to synchronize single-cell oscillators with each other, the mammalian circadian system is organized in a hierarchical manner. A master clock resides in the suprachiasmatic nuclei (SCN) of the hypothalamus (Moore and Eichler, 1972; Ralph et al., 1990; Stephan and Zucker, 1972). The SCN receive light information from melanopsin-expressing cells in the retina via the retino-hypothalamic tract (Provencio et al., 2000). Time information is then passed on to subordinate peripheral tissues via humoral and neuronal signals (Buijs et al., 2003; Liu et al., 2007; Welsh et al., 2004; Yoo et al., 2004). In this way all peripheral and non-SCN tissue clocks are coordinated by the master clock.

2. Role of glucocorticoids in clock regulation

Among all peripheral oscillators, the adrenal gland holds a special role since the adrenal circadian clock can influence rhythms in other peripheral tissues via rhythmic release of hormones with clock-modulating properties. The adrenal gland is composed of an outer cortex and an inner medulla. The medulla releases catecholamines (epinephrine and norepinephrine), whereas the cortex secretes mineralocorticoids from the outer *zona glomerulosa*, glucocorticoids (GCs) from the intermediate *zona fasciculata*, and sex steroids from the inner *zona reticularis*. Cortisol and corticosterone, the main GCs in humans and rodents, respectively, display a very robust circadian oscillation with blood levels peaking shortly before the onset of the active phase (i.e. the early morning in humans and the early evening in nocturnal rodents). The circadian GC rhythm is overlaid by strong ultradian pulsatility with a period of around one hour and an amplitude that varies considerably during the day (Windle et al., 1998). GCs are secreted upon adrenocorticotropic hormone (ACTH) binding to melanocortin-2 receptors (MC2R) in the adrenal gland. ACTH itself is secreted from the anterior pituitary upon corticotrophin releasing hormone (CRH) signaling, which stems from the paraventricular nucleus (PVN) of the hypothalamus. Together, these tissues and factors constitute the hypothalamus-pituitary-adrenal (HPA) axis. Circadian oscillations are detectable for all components (CRH, ACTH, and GCs) (Chrousos, 1998; Girotti et al., 2009). However, it is not clear if rhythmic HPA axis activity is necessary for the circadian rhythm of GC secretion. On one hand, adrenal rhythms persist after hypophysectomy, when no ACTH is present (Fahrenkrug et al., 2008). On the other hand, ACTH is capable of phase-dependently resetting GC rhythms (Yoder et al., 2014). In addition, the HPA axis gets direct input from the SCN via the paraventricular nuclei of the hypothalamus (Dickmeis et al., 2013; Vrang et al., 1995) and the SCN controls GC rhythms as was shown in SCN-lesioned animals (Moore and Eichler, 1972). The circadian pattern of GC secretion can be abolished by specifically disrupting the circadian clock in the adrenal gland (Oster et al., 2006a; Son et al., 2008), indicating that this peripheral tissue clock finally governs GC secretory patterns.

Glucocorticoids act via mineralocorticoid (MR) and glucocorticoid receptors (GR), type-1 nuclear receptors with broad expression patterns throughout the body except for the SCN. GR signaling can mediate phase resetting of peripheral clocks, pointing at a special role of GC rhythms in the coordination of the organism's circadian network (Balsalobre et al., 2000). For instance, microarray analysis of murine liver revealed 100 rhythmic genes whose oscillation was directly dependent on adrenal signals, because rhythmicity of these genes is lost in adrenalectomized animals (Oishi et al., 2005). Finally, in a mouse model of *jet lag*, which is caused by an abrupt phase shift of light conditions, GC rhythms can modify the kinetics of entrainment to the new time zone (Kiessling et al., 2010).

On top of their phase shifting ability, GCs can stabilize peripheral rhythms against external perturbation. Timed food restriction can induce phase shifts in peripheral tissues so that peripheral clocks become uncoupled from the master clock in the SCN that stays tied to the light-dark cycle. The circadian system is more robust against such perturbations when GCs are high (Le Minh et al., 2001). In summary, rhythmic GC secretion is an important timing signal for the coordination of peripheral clocks.

3. Neurobiology of stress (HPA axis, glucocorticoids, catecholamines)

Besides their role in circadian coordination GCs are important vectors of the stress system. Stress refers to an external or internal

challenge that requires an adequate reaction of the organism in order to survive or, in less drastic cases, to avoid pain or discomfort. An elaborate response system has evolved that becomes activated when the organism is exposed to stress. It involves an immediate response via activation of the autonomous nervous system (ANS) and a delayed response via HPA axis-mediated release of GCs (Ulrich-Lai and Herman, 2009).

All sensory systems can collect information about stressful events (e.g. a decrease in blood volume, changes in blood composition, or the encounter of a predator) and forward this information to the brainstem (Ulrich-Lai and Herman, 2009). From here, subsequent activation of the ANS and the HPA axis is regulated. In case of the HPA axis, stress-mediated activation triggers the production and release of GCs in the adrenal gland. Stress signals from the hippocampus, prefrontal cortex or amygdala are transferred to the paraventricular nucleus (PVN) of the hypothalamus to stimulate the secretion of CRH to initiate HPA axis activation. The fact that GCs need to be newly synthesized after each trigger leads to a certain delay in the final effector response. Therefore, the dynamics are slower (in the range of minutes) compared to ANS activation, which occurs within seconds after stress initiation.

Exposure to a stressor results in an immediate increase of catecholamines via activation of sympathetic preganglionic neurons in the spinal cord (Nygren and Olson, 1977; Westlund et al., 1983). From here, the signal is either transferred to postganglionic neurons projecting to peripheral effector organs where they are translated into the classical *fight-or-flight response* (e.g. increase of heart rate and blood pressure, vasoconstriction, stimulation of sweat glands, energy mobilization etc.) or preganglionic nerves continue as splanchnic nerves to peripheral effector organs. As such, splanchnic nerves constitute a short-cut to the adrenal medulla where the immediate release of catecholamines is initiated (Holgert et al., 1998). The acute stress response is terminated by reflex parasympathetic activation and negative feedback inhibition from GCs that stop the release of CRH and ACTH from hypothalamic and pituitary cells, respectively (Nader et al., 2010).

Even though the ANS and the HPA axis are two different branches within the general stress system and their dynamics are quite different, both act together to coordinate an appropriate response to stress. For the response to certain stressors, for example, HPA axis activation is supported by noradrenergic and adrenergic projections from the hindbrain to the PVN. As such, lesion experiments have shown that stress-induced GC release can be impaired when these projections are not functional (Ritter et al., 2003). Conversely, cells in the inter-mediolateral column receive input from the PVN, suggesting that signals from the hypothalamus can modify the autonomic stress response (Tucker and Saper, 1985).

Both circadian and stress-mediated aspects play an important role in regulating HPA axis activity and GC levels. In case of catecholamines, it is technically difficult to assess to which extent the circadian clock influences catecholamine levels. However, a circadian oscillation of serum levels of epinephrine and norepinephrine has been described (Dimitrov et al., 2009). At the same time, GC secretion can be influenced by SCN-sympatho-adrenal innervations (Ishida et al., 2005; Ulrich-Lai et al., 2006) and ACTH from the HPA axis can stimulate (nor)epinephrine secretion (Valenta et al., 1986) so that ANS and HPA axis are interconnected also for circadian aspects.

In conclusion, both HPA axis and ANS show aspects of circadian and stress-mediated regulation and they interact on several levels (Fig. 1). In the following, we will highlight how the circadian system and stress response influence each other in rodents. Finally, we propose how this knowledge might be used for translational approaches.

4. Circadian gating of stress responses

Stress impairs the body via a complex network of interacting signaling cascades regulating the vulnerability to and severity of stress. In principle, one has to distinguish between the acute stress response preparing the body for rapid action and repeated stress inducing broader alterations and adaptations, which are associated with changes in energy metabolism and an elevated risk for psychiatric disorders.

While it is known since the 1970s that the responsiveness of HPA axis is modulated by the time of day (Dunn et al., 1972b; Gallant, 1979; Gibbs, 1970; Kant et al., 1986; Torrellas et al., 1981; Zimmermann and Critchlow, 1967), we are far away from understanding the underlying mechanisms. Disruptions of the circadian clock are associated with altered HPA axis activity and GC concentrations as well as with metabolic impairments and major depression (Albrecht, 2010; Barclay et al., 2012; Leliavski et al., 2014; Mukherjee et al., 2010; Turek et al., 2005). However, only little is known about stressor exposure in clock gene mutant mice. So far, we know that the impact of a clock gene deletion on circulating GCs is depending on which aspect of the clock feedback loop is affected. Mice with a clock gene mutation in the positive limb of the oscillator, *Bmal1* or *Clock*, consistently suffer from hypocortisolism (Leliavski et al., 2014; Turek et al., 2005) while *Cry* mutations (affecting the negative limb) lead to hypercortisolism (Barclay et al., 2013; Lamia et al., 2011) associated with a reduced genotoxic stress response. However, the deletion of *Per2*, which also affects the negative limb, results in hypocortisolism (Yang et al., 2009). Further, the deletion of *Per* leads to increased immobilization, stress-induced grooming, and nociceptive behaviors associated with increased CRH expression in the PVN of those mice (Zhang et al., 2011). *Immobilization stress* and *genotoxic stress*, however, affect the body in mechanistically different ways. Responses to swim stress, which is mechanistically comparable with *immobilization stress*, is reduced in *Bmal1* knockout mice leading to the assumption that the manipulation of the positive and negative limb of the core clock feedback loop has opposing effects on stress regulation. However, a general statement about stress responsiveness in clock gene mutants is, due to the small number of studies so far, not possible and more comparable experiments are needed to

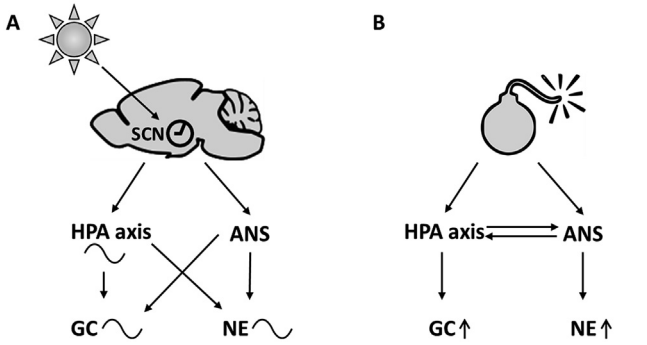

Fig. 1. The HPA axis and the autonomous nervous system receive circadian and stress-induced input and influence each other. A) The central circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus is entrained by light. Neurons from the SCN project to the hypothalamic-pituitary-adrenal (HPA) axis, and induce a rhythmic hormone secretion that ultimately stimulates rhythmic GC production in the adrenal gland, as indicated by the sine waves. At the same time, SCN projections reach the autonomic nervous system (ANS), resulting in rhythmic norepinephrine (NE) and epinephrine (E) output at the adrenal medulla and cortex. In addition, ANS innervation of the adrenal gland influences GC rhythms and the HPA axis also stimulates the release of NE and E. B) Stress activates both the HPA axis and the ANS, stimulating the release of GCs and catecholamines. HPA axis and ANS are interconnected so that both systems interact during the stress response.

close this gap. Further, the circadian machinery is not completely disrupted by the deletion of only one of the *Cry* or *Per* gene, increasing the difficulty to draw a conclusion on clock impact from those studies.

Interestingly, BMAL1 and CRY do not only have opposing functions in the TTL, both interact with the HPA axis at different levels and affect different aspects of the stress response (Lamia et al., 2011; Leliavski et al., 2014), fine-tuning the responsiveness of the system to stress-related stimuli along the course of the day (Fig. 2). In male mice as well as in female rats, adrenal ACTH sensitivity is elevated during the active phase (Bartlang et al., 2012; Engeland et al., 1977; Leliavski et al., 2014; Oster et al., 2006b). A deletion of the core clock gene *Bmal1* leads to time independent and low ACTH sensitivity, which is comparable with that of wildtype animals during the day. This results in a lower depression-like behavior in the forced swim test paradigm (Leliavski et al., 2014). GR sensitivity, which is essential for feedback inhibition of the HPA axis, is also regulated by the circadian system (Lamia et al., 2011). CRY1 and 2, expression of which peaks in the early night, interact with the C-terminus of GR, which is also required for ligand binding. In this way, CRY1 and 2 oppose GR activation. Genetic deletion of both *Crys* leads to non-oscillating and elevated GC levels due to impaired feedback inhibition (Lamia et al., 2011). In summary, clock mediated increased HPA axis sensitivity during the active phase together with elevated ACTH sensitivity (Leliavski et al., 2014; Oster et al., 2006b) and simultaneous repression of GC-mediated feedback inhibition (Lamia et al., 2011) drive time-of-day dependent responsiveness to stressor exposure.

At the time when the HPA axis is most sensitive to stimulation, *physical stressor* exposure like *hemorrhage* (Lilly et al., 2000), *hypoglycemia* (Kalsbeek et al., 2003), or *oxidative stress* (Antoch et al., 2005; Fanjul-Moles and Lopez-Riquelme, 2016) yield a greater increase in circulating GCs than at other periods of the day. However, during the inactive phase, when the HPA axis should be less responsive, *restraint/immobilization*, *foot shock*, or *shaking stress* result in a stronger increase in GC and ACTH release, and blood pressure (Bernatova et al., 2002; Bradbury et al., 1991; Gattermann and Weinandy, 1996; Gutierrez-Mariscal et al., 2012; Mathias et al., 2000; Retana-Marquez et al., 2003; Torrellas et al., 1981). More experiments are needed to clarify, how time-of-day affects the responsiveness to stress. Differences in experimental setups (e.g. different water temperatures in the *forced swim test* (Bachli et al., 2008)) may explain some of the discrepancies between studies (Retana-Marquez et al., 2003). In addition, species (e.g. rats vs. mice) or gender differences (see below) may further play a role.

5. Sex differences in acute stress responsiveness

Experiments investigating the circadian aspect of stress have so far mainly used male mice or rats. While elevated ACTH sensitivity during the active phase is comparable in males and females (Engeland et al., 1977), endogenous GC levels are significantly elevated (in an estrus-dependent way) in females as compared with males and many stress responses are fundamentally different between genders (Griffin and Whitacre, 1991; Jezova et al., 1996; Joffe et al., 1976; Turner, 1992; Young, 1998). The function of GR in the forebrain, for instance, shows strong gender differences (Solomon et al., 2012). While Gattermann and Weinandy did not detect sex differences in the response to different stressors at the level of GC release in rats (Bohacek et al., 2015; Gattermann and Weinandy, 1996), several studies point to a higher vulnerability to certain stress-related neuropsychiatric diseases in females (Palanza, 2001). In female mice, *cold water swim stress* leads to elevated neuronal activity and hippocampal responses in female

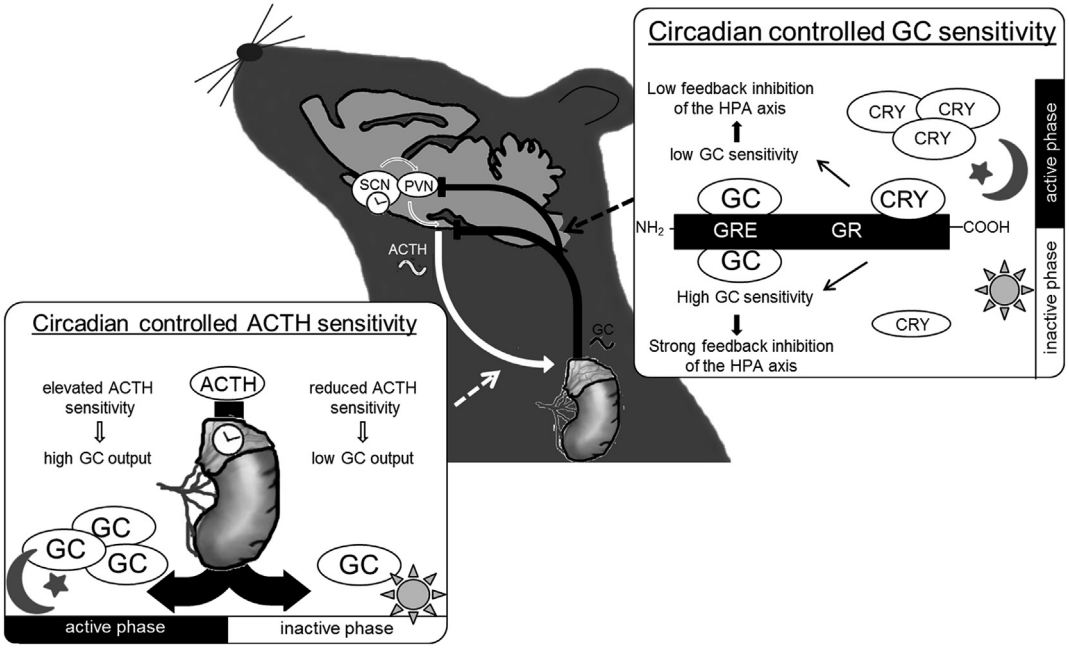

Fig. 2. Circadian control of HPA axis responsiveness in nocturnal rodents. The circadian clock controls several aspects of the hypothalamus-pituitary-adrenal (HPA) axis leading to an increased HPA axis responsiveness during the active phase. In unstressed conditions, the master pacemaker located in the suprachiasmatic nucleus (SCN) promotes rhythmic release of adrenocorticotropic hormone (ACTH) from the pituitary into the circulation to stimulate adrenal glucocorticoid (GC) production in a time-of-day-dependent manner (white). Rhythmically secreted GCs, in turn, inhibit the activation of the HPA axis via negative feedback (black). Beside this general mechanism, adrenal ACTH sensitivity is under circadian control and increased during the active phase leading to a high GC output (scheme lower left). In line with the increased adrenal ACTH sensitivity during the night, central GC sensitivity varies also over the course of the day. CRY1 and CRY2 suppress GC-mediated feedback inhibition via binding to the C-terminus of glucocorticoid receptor (GR). Thereby, GCs cannot repress HPA axis activity by binding to the glucocorticoid response element (GRE) during the night further promoting an increased sensitivity of the HPA axis (scheme upper right).

mice (Bohacek et al., 2015; Dubreuil et al., 1986), indicating that different types of stressors are differentially regulated. Sexual dimorphisms in stress responses in the mesolimbic system further complicate the picture (Trainor, 2011; Westenbroek et al., 2003). Whether the circadian system is involved in those gender effects is not known. Chronobiological research traditionally relies on males – largely because of an increased stability of male running-wheel behavior – and many of the rare studies in females are poorly compared to those in males. More research on that topic is needed, especially against the background of an increased vulnerability of females to certain stress paradigms.

6. Circadian regulation of chronic stress

In contrast to acute stress, chronic or repeated exposure to a stressor leads to lasting adaptations of the body, e.g. in energy metabolism, and may favor the development of metabolic or psychiatric disorders, both in humans and in rodents (Foster and Kreitzman, 2014; Jones and Benca, 2015; Kudryavtseva et al., 1991; Rygula et al., 2006). Studies addressing the impact of social stress paired with circadian rhythm disruption are therefore of high clinical interest. Unfortunately, many studies still do not disclose the time of stressor exposure and only few studies directly compare the impact of a stressor at different times of the day. Gattermann and Weinandy have shown that the type of stressor is essential for the nature of the stress response (Gattermann and Weinandy, 1996) and it is, thus, often difficult to compare published studies due to a lack of normalized stress paradigms. In rats repeated stress has a more detrimental impact if applied during the inactive phase compared with the active phase. *Chronic mild stress*, a paradigm in which different types of unpredicted stressor exposure are applied over several weeks, leads to depressive and anxiety-related behaviors if applied at day, but not during the night (Aslani et al., 2014). Unfortunately, the post-stress analyses were performed during the day only. Whether the nighttime stress group will show depressive and anxiety-related behaviors at times stress was applied, needs to be evaluated (Aslani et al., 2014). Stress induced by *cat smell*, *immobilization stress*, or *tail shocks* has also a more detrimental impact when repeatedly applied during the inactive phase (Cohen et al., 2015; Fonken et al., 2016; Retana-Marquez et al., 2003).

In modern human societies, however, stress origins predominantly from social interactions and usually involves little psychological action. A common animal model for social stress with good translational relevance is the *social defeat stress* test (also known as *resident-intruder paradigm*) whereby the experimental mouse (intruder) is placed for a specific time into the cage of a superior resident, resulting in a subordination involving physical and social stress and mimicking social conflicts in humans. While most of these studies point to a more detrimental effect of nighttime stress in mice (Bartlang et al., 2012, 2015, 2014), metabolic effects are predominantly observed as a response to stress during the inactive phase (Rybkin et al., 1997) or as a response to full-time stress (Harris, 2015; Ramirez-Zacarias et al., 1992). Stress during the active phase, however, does not affect bodyweight in rats (Gorka and Adamik, 1993), pointing to a circadian stress response gating. Classical studies employing this paradigm argue against acclimatization to chronic *social defeat stress* (Tornatzky and Miczek, 1993). However, more recent studies reveal adaptions to repeated *social defeat stress* at the previous time of stress, which, in mice, occur more frequently during the active phase (Bartlang et al., 2012, 2015, 2014). A weakness of this paradigm is the reduced stress response of females due to their poorly developed territorial behavior (Haller et al., 1999). Therefore a related paradigm (*social instability paradigm*) was developed in which females undergo an alternating housing paradigm with a single housing isolation phase followed by mixed-sex crowding phases meant to induce social instability (Haller et al., 1999).

Unfortunately, most stress studies are performed during normal lab working hours which usually coincides with the inactive phase of nocturnal rodents, and only very few studies are available that directly address time-of-day dependent effects. The inherent complexity of social stress paradigms and the non-optimal control for circadian effects may partly explain why results from acute as well as repeated stress paradigms appear sometimes contradictory. More uniform stress protocols and a clearer discrimination of parameters such as mouse strains, gender and timing should improve our understanding of the underlying mechanisms.

7. Circadian disruption as stressor

Besides these *classical stressors*, also circadian disruption, e.g. induced by environmental factors such as *constant light exposure*, can be considered as stressor since it alters catecholamine and GC release. Considering that circadian rhythm disruptions become more and more frequent with increasing shift work, it is important to recognize that those also affect HPA axis activity and may contribute to a broad range of stress-related disorders. To distinguish circadian disruption stress from more *classical stressors*, we will refer to it as *circadian stressor*. The most potent *circadian stressor* is light. A short *light pulse* administered to rodents during the subjective night can elicit a plasma corticosterone increase 60 min after onset of stimulation. This increase has both been described as ACTH-independent in mice (Ishida et al., 2005), as well as having an ACTH-dependent contribution via the HPA axis in rats (Mohawk et al., 2007). Repetitive changes in the daily light onset (*jet lag paradigm*), *dim daylight illumination* or *constant light* are associated with hypercortisolism (Dunn et al., 1972a; Sakellaris et al., 1975) and a suppressed response to further acute stress stimuli (Sakellaris et al., 1975). Light, however, does not exclusively evoke hypercortisolism. A 1-h shortening of the diurnal period (9.5 h light: 13.5 h dark) leads to dampened circulating GCs profiles uncoupled from adrenal ACTH responsiveness, which stays aligned to the SCN clock and behavior (Sollars et al., 2014). The consequences of this HPA axis misalignment for further stress responses have not yet been investigated.

A second potential *circadian stressor* is *food*. Food intake at a non-natural circadian phase alters the rhythm of GC release. In mice, daytime restricted feeding promotes a second peak in circulating GC levels during the day (Luna-Moreno et al., 2012). In summary, *chronic circadian disruptions*, induced by frequent mistimed light exposure or food intake, can potently alter the diurnal level of secreted GCs and stress-induced GC responses. Interestingly, circadian disruptions and repeated stressor exposure have comparable pathological consequences, ranging from compromised immune responses (Castanon-Cervantes et al., 2010), mood and cognitive disorders (Gibson et al., 2010; LeGates et al., 2012), the development of metabolic disruption (Barclay et al., 2012; Marcheva et al., 2010; Turek et al., 2005), accelerated tumor growth and increased de-novo carcinogenesis (Filipski et al., 2004; Van Dycke et al., 2015), to accelerated aging (Kondratov et al., 2006) and hastened death (Davidson et al., 2006). However, whether GC deregulation provides the causal link between circadian disruption and the aforementioned pathologies is still unclear. As an example, the metabolic phenotype resulting from chronic circadian disruption matches that of GC excess (Nader et al., 2010). However, since key downstream targets of metabolic pathways can both be affected by GCs and the circadian clock, it is equally possible that they act independently of each other.

8. Stress influences clock function

As described above, the effectors of the stress system also impinge on circadian regulation. GCs and epinephrine can act as synchronizers of circadian tissue clocks (Akiyama et al., 2003; Balsalobre et al., 2000; So et al., 2009b), but there are numerous additional ways how stress affects the circadian system. The effectors of the stress response act via specific receptors. In the case of GCs, this is mainly GR, as MR is bound by GCs even at the nadir of the GC circadian rhythm, which makes MR signaling inefficient in conveying time-of-day information. GR is ubiquitously expressed in nearly all tissues and organs (Chrousos and Kino, 2005; Kino and Chrousos, 2004; Nader et al., 2010) with notable exception of the SCN where no GR expression was detected (Balsalobre et al., 2000). In consequence, the SCN is exempt from direct feedback synchronization by GCs.

For GR signaling, there are several classical pathways that influence gene expression and non-classical, non-genomic signaling (Fig. 3) (Beato et al., 1987; Freedman, 1992; Groeneweg et al., 2012). Among the classical signaling pathways, GR dimers can interact with glucocorticoid response elements (*GREs*) that are located in regulatory regions of GC target genes. GR binding activates transcription of these genes. For instance, *GREs* have been identified in some clock genes (So et al., 2009a). Furthermore, GRs can interact with other transcription factors such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1), or STAT5. This also activates transcription of target genes (Chrousos and Kino, 2005; De Bosscher and Haegeman, 2009; Garside et al., 2004; Kino and Chrousos, 2004; Scheinman et al., 1995). In addition to transactivation, there is also the possibility of transrepression of specific negatively regulated genes mediated by the binding of GR to *negative GREs* (*nGREs*) (Surjit et al., 2011). Lastly, there is a third option for transcriptional regulation by GR action whereby GR interaction with DNA influences neighboring DNA-bound transcription factors (Groeneweg et al., 2012; Samarasinghe et al., 2012). Activation of these classical GR signaling pathways takes minutes to hours. In contrast to that, non-classical GR signaling acts independently of transcription and gene expression so that the resulting response is much faster (seconds to minutes) (Groeneweg et al., 2012). GR non-genomic signaling acts by altering activity of various kinases, such as phosphoinositide 3-kinase (PI3K), AKT, and mitogen-activated protein kinases (MAPKs). With that, these different pathways contribute to the high complexity and diversity of the biological action of GCs. In situations of acute stress, non-genomic signaling pathways are assumed to be more pronounced because responses have to be fast. In contrast, genomic signaling pathways seem to rather mediate chronic stress responses and long-term adaptations to increases in GC concentrations. In the future, selective modulators of the GR-dependent non-genomic or genomic pathways may allow for a more specific modulation of the GC system in therapeutic applications (Oakley and Cidlowski, 2013). It is not known if non-genomic GR signaling impinges on circadian clock function, but target proteins such as MAPKs have been shown to affect clock function in various contexts (Akashi and Nishida, 2000; Butcher et al., 2002).

Many studies in rodents have addressed the influence of stress on circadian rhythms. Using a *social defeat paradigm*, Tahara et al. reported that stress in the beginning of the light phase causes a phase advance shift in mRNA expression rhythms of several core clock genes in peripheral organs in mice (Tahara et al., 2015). When mice were stressed at other times during the day, the effect was a phase delay or even loss of synchrony, indicating that the influence of stress on peripheral clocks is time-of-day dependent. The stress paradigm included *social defeat* on three consecutive days, which the authors call *sub-acute*. Interestingly, the effects were milder or undetectable after chronic exposure to the stressor over several weeks, pointing at habituation effects. For the SCN pacemaker no changes were reported in this study, in line with the reported absence of GR expression in this tissue. In a more chronic approach, the consequences of repeated *social defeat* for 19 days, either during early light or early dark phase, were analyzed (Bartlang et al., 2014). When stress was applied during the early dark phase, the amplitude of *Per2* oscillations in the SCN increased, while *Per2* and *Cry1* expression was downregulated in the adrenal gland. Conversely, stress in the early light phase did not affect the SCN clock, but led to a phase advance of the adrenal oscillator. Compared to the study from Tahara et al. (Tahara et al., 2015), the phase shifts reported for the adrenal clock were similar. Interestingly, it appears that in the chronic paradigm the SCN clock is affected by stress, probably reflecting indirect mechanisms. In a third study Razzoli et al

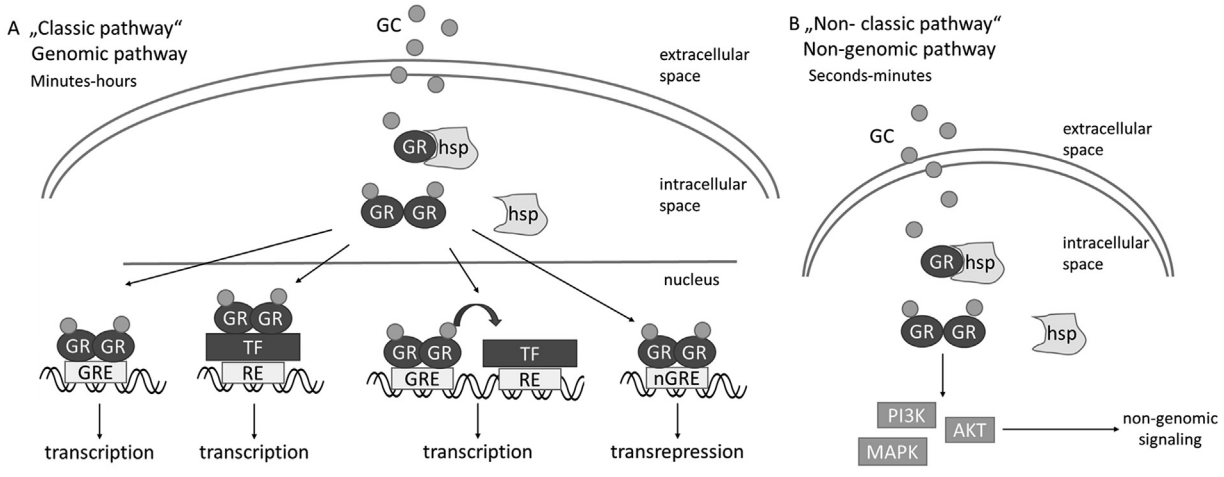

Fig. 3. GC signaling downstream of GR. A) GCs bind to intracellular nuclear receptors (GR, but also MR) to activate or repress transcription. GCs diffuse through the cell membrane and bind to cytoplasmic receptors (GR). This binding mediates dissociation of GR from heat shock proteins (hsp) and dimerization of GR molecules bound to GC. GR/GC complexes translocate into the nucleus where they bind to (negative) glucocorticoid response promoter elements (*(n)GRE*) and activate transcription or they bind to nGRE, leading to transrepression. Alternatively, they associate with other transcription factors (TF) and influence their action on corresponding responsive DNA elements (RE). B) Via non-classical signaling, GR dimers can also directly modify the activity of kinases such as phospho-inositol 3 kinase (PI3K), AKT, or mitogen activated protein kinase (MAPK), independent of genomic events.

(Razzoli et al., 2014). compared a single *social defeat stress* with chronic stress across two weeks (stressor applied during early light phase). Here, both single and repeated stress phase advanced the clock in the adrenal gland, while chronic exposure to the stressor phase additionally shifted the clock in the pituitary. In addition to direct effects on molecular circadian oscillations, social stress in the beginning of the dark phase was shown to influence the activity rhythm as an output of the circadian clock (Bartlang et al., 2015).

Surprisingly, long-term effects of repeated stress on clock function appear minor. Endo and Shiraki (Endo and Shiraki, 2000) exposed rats to *foot shocks* or *psychological stress* in the end of the light phase over twelve weeks. Two to three months after stress no effect on circadian activity, body temperature, or feeding and drinking behavior could be observed. Only core body temperature was slightly elevated in the previously stressed group (Endo and Shiraki, 2000).

Of note, the studies summarized here were either performed only with male animals or they did not detect changes between males and females. However, as mentioned above, there are some general gender-specific differences in the GC system. Female mice have higher baseline serum corticosterone concentrations, higher stress-induced corticosterone, and heavier adrenal glands than male mice (Malisch et al., 2007). Most likely, sex hormones are involved in these differences. While estrogens were described to stimulate HPA axis activity, either by increasing secretion of corticosterone itself or by reducing central negative-feedback sensitivity, androgens generally have a suppressive effect on the HPA axis (Handa et al., 1994).

9. Translational considerations

9.1. Health consequences of the 24-h society

A hallmark of modern societies is the uncoupling of the sleep-wake cycle from natural light conditions, made possible by the invention of the electric light. Modern airplane transportation allows rapid transcontinental travel resulting in a desynchronization between external and internal time termed *jet lag*. An increasing prevalence of shift work in an industrialized environment leads to mistimed sleeping and eating cycles, leading to what Till Roenneberg has coined as *social jet lag* (Foster and Kreitzman, 2014; Wittmann et al., 2006). While all these factors can count as stressors in themselves, socioeconomic variables may act as further reinforcers.

Rhythm disruptions bear wide-ranging consequences on human health (Jones and Benca, 2015; Li et al., 2011). Even after short-term circadian misalignment protocols (8 days), human subjects show higher blood glucose and insulin levels as well as elevated blood pressure, which are markers for metabolic and cardiovascular disease, respectively (Scheer et al., 2009). This translates into a higher incidence of obesity, diabetes type II and related metabolic disturbances (Karlsson et al., 2003; Pan et al., 2011; Proper et al., 2016), along with hypertension (Kubo et al., 2013), coronary heart disease (Vetter et al., 2016), and ischemic stroke (Vyas et al., 2012) in shift workers. Finally, modest, yet significant increases of risk (RR < 1.5) can be observed for breast cancer in chronic shift workers and flight attendants (He et al., 2015). In consequence, the International Agency for Research on Cancer has classified shift work as a potential carcinogen (Straif et al., 2007).

Work on animal models has shown that circadian disruption or frequent exposures to stress are prominent mediators for the development of depression-like behavior (Benedetti et al., 2007; Kudryavtseva et al., 1991; Li et al., 2009; Partonen et al., 2007; Roybal et al., 2007; Rygula et al., 2006). While the impact of stressor exposure on psychiatric disorders is similarly seen in humans, the metabolic impact of stress in humans and rodents is difficult to compare since rodents are mostly under well controlled feeding regimes (see below) (Harris, 2015; Nyberg et al., 2012). This raises the question to which extent the molecular mechanisms are differentially regulated in humans or whether important parameters were overseen so that results from rodents cannot be translated to humans.

9.2. Benefits and limitations of animal studies in circadian and stress research

Several rodent animal models have been employed to study the effects of circadian disruption and stress on numerous diseases, including metabolic, cardiovascular, and psychiatric disorders. The circadian clock and the stress system are largely conserved between rodents and humans, indicating that this might also be true for the pathological effects. Key advantages of animal models include the high level of control over parameters to be manipulated or measured and the applicability of invasive techniques. This offers unparalleled insight into the fundamental molecular and physiological mechanisms at work. As mentioned above, the extent to which the results are relevant for humans can vary, indicating that careful optimization of animal models and experimental setups is crucial to achieve results that are meaningful for humans. In addition, standardized tests for rodents reduce the complexity of parameters in the experiment, but it has to be considered that a stressful situation for humans is often everything but simple. Moreover, the complexity of the situation – leading to a perceived helplessness in the affected person – may actually be key to its stressful nature (Cohen et al., 2007). Animal studies frequently investigate circadian disruptions induced by genetic modification of clock genes. These studies are essential to understand molecular mechanisms. However, humans mainly suffer from circadian disruptions induced by environmental factors. Therefore, a focus on animal models with external circadian rhythm perturbations (induced by, i.e., shifted light-dark cycles, sleep restriction, or mistimed feeding) might be more useful for translational approaches.

Clearly, as mentioned above, chronic stress in humans is in most cases of a psychological nature and heavily depends on social context and personality (for review see (Cohen et al., 2007; Harris, 2015)). Humans may worry about potential future conflicts much more then mice do, leading to a different type of stress response that may affect other brain regions than in rodents, that arguably respond primarily to acute perceived stress involving fear and a struggle for life. As one example, the impact of stress on energy homeostasis is different between humans and rodents. While rodents mostly lose weight when exposed to chronic stress, humans mainly suffer from excessive appetite for palatable food and increased body weight gain (Harris, 2015; Nyberg et al., 2012). Several studies addressing the interaction of social stress and the reward system point to an increased demand to rewarding components (Fisher et al., 1978; Hymel et al., 2014) indicating a switch in the reward circuit promoting overeating of palatable nutrients, if available (Roberts et al., 2014; Rutters et al., 2009). Interestingly, when stress-exposed rodents have access to a high-caloric diet they consume significantly more than on a standard chow. In consequence, they show a similar body weight gain as seen in humans (Chuang et al., 2011). This shows that a thorough study design is essential to achieve results that are translatable to humans.

Besides a uniform study design reflecting the human situation as much as possible in terms of stressor exposure and circadian disruptions, one has to consider different regulatory mechanisms due the different activity patterns and endocrine regulation. In contrast to commonly used rodent models, which are mostly

nocturnal, humans are active during the light phase. The rhythms of circulating GCs and catecholamines in rodents as well as in humans are associated with the activity pattern (rodents: (Agren et al., 1986; Manshardt and Wurtman, 1968); humans: (Burgess et al., 1997; Scheer et al., 2003)). However, clock gene expression in humans and rodents is in phase and, thus, downstream rhythms must be differentially regulated. Therefore, comparative studies investigating the underlying mechanisms in diurnal rodents may improve our understanding of human regulatory mechanisms. Another important point for the translatability of mouse studies in particular is the lack of melatonin. In humans, melatonin has been shown to influence cortisol peaks at the beginning of the day. Most standard mouse inbred strains, however, are melatonin deficient (Kasahara et al., 2010) which complicates the translatability. Studies investigating HPA axis regulation in melatonin will help to understand the interaction of circadian clock and stress axis regulation in humans.

In summary, species differences between humans and rodents can complicate the interpretation of results derived from animal studies, but animal models are still indispensable to elucidate molecular mechanisms and for invasive manipulations. A careful optimization of experimental conditions will maximize the relevance of animal work for the human situation.

9.3. *Stress chronotherapy*

Circadian disruptions and frequent exposure to stressors promote or amplify a broad range of health disorders. Therefore, a reduction of, both, *circadian* and *classical stressors* would improve health and quality of life. However, this is often difficult to achieve so that strategies stabilizing endogenous rhythms to counteract circadian perturbations would be highly beneficial. Some circadian disruptions can be corrected without great efforts. For instance, mistimed light exposure of non-shift-working people can be avoided by lightproof curtains and reduced blue light illumination in the evening (*dark therapy*). Spectral filters or apps can extract blue light, which has a strong clock-modulating capacity, from TV or computer screens. Regular exposure to daylight or a daylight lamp in the morning as *light therapy* can stabilize circadian rhythms and was already shown to improve major depression in humans (Lewy et al., 1998, 1982, 1987). Furthermore, mistimed feeding as *circadian stressor* adversely affecting circulating GCs can be reduced with scheduled meals. Food as well as scheduled activity during the natural activity phase enhances the circadian alignment of peripheral tissue clocks with the central master pacemaker (Otsuka et al., 2015). However, ~30% of employees in health care are shift working and suffer from circadian disruptions (Arendt, 2010). For those, a stabilization of the circadian rhythm is not as easily achieved as described above (Lowden et al., 2010). While in rodents a regulated access to food during the active time normalizes circadian misalignment induced by shift work (Barclay et al., 2012), a regulated meal schedule may promote hypoglycemia and increased accident risks in shift working humans. Two studies describe an alternative approach for those cases: subjects were exposed to daylight or blue light in the evening to activate the clock. In the morning, daylight exposure was minimized by lightproof curtains, sunglasses and others (Arendt, 2010; Stevens et al., 2007). Thereby the circadian clock was more primed to the nighttime work and health problems were reduced.

10. Conclusions

It is getting more and more appreciated that the circadian clock is influencing physiology and behavior on many different levels promoting a number of diseases in asynchronous conditions. Unfortunately, circadian misalignment is getting more and more common. Late night or evening shopping, off-shift work, or nighttime illumination increases circadian disruption in humans. On top of that, modern professions often come along with a high stress level, further amplifying the susceptibility to health disorders.

In rodents, the connection between circadian system and stress response is well characterized, even though differences in study paradigms sometimes complicate general conclusions. Nevertheless, it can be said that the stress responsiveness varies over the course of the day and that, *vice versa*, stress is able to affect the regulation of the circadian clock. With this knowledge, it should be possible to devise better recommendations for the timing of working hours, stressful meetings, and rest phases to increase productivity and life quality, while reducing the therapeutic costs for work related disorders.

Declaration of conflicting interests

The authors declare that there is no conflict of interest with respect to their authorship or the publication of this article.

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