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The impact of stress and stress hormones on endogenous clocks and circadian rhythms

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ABSTRACT

In mammals, daily rhythms in physiology and behavior are under control of a circadian pacemaker situated in the suprachiasmatic nucleus (SCN). This master clock receives photic input from the retina and coordinates peripheral oscillators present in other tissues, maintaining all rhythms in the body synchronized to the environmental light–dark cycle. In line with its function as a master clock, the SCN appears to be well protected against unpredictable stressful stimuli. However, available data indicate that stress and stress hormones at certain times of day are capable of shifting peripheral oscillators in, e.g., liver, kidney and heart, which are normally under control of the SCN. Such shifts of peripheral oscillators may represent a temporary change in circadian organization that facilitates adaptation to repeated stress. Alternatively, these shifts of internal rhythms may represent an imbalance between precisely orchestrated physiological and behavioral processes that may have severe consequences for health and well-being.

1. Introduction

In mammals, daily rhythms are observed in almost every function and process, ranging from overt behaviors such as locomotor activity, sleep and feeding to physiological measures such as heart rate, body temperature and hormone release. In most cases these daily rhythms are driven by endogenous biological clocks, or oscillators, that reside in different tissues of the body (Dibner et al., 2010; Mohawk et al., 2012; Reppert and Weaver, 2002).

In the early 1960s, Curt Richter, at the Johns Hopkins Medical School in Baltimore, demonstrated that blinding rats, and thereby disconnecting them from the environmental light-dark cycle, resulted in free running activity rhythms with periods that were most often slightly shorter or longer than 24 h (Richter, 1967; see Fig. 1 for circadian terminology). According to his narratives, the clock system driving these endogenous activity rhythms were largely unaffected by ablation of almost every part of the brain. However, when he lesioned the hypothalamus, rhythmicity in activity ceased to exist and all locomotor activity, feeding and drinking became evenly distributed across the 24 h cycle (Fig. 2). Later studies identified the suprachiasmatic nucleus (SCN), a sub-region of the hypothalamus situated above the optic chiasm, as the critical locus of this lesion effect (Moore and Eichler, 1972; Stephan and Zucker, 1972). The role of the SCN as a true circadian clock and pacemaker for many rhythms was then established over the next two decades by a variety of different approaches, including electrophysiological measurements and transplant studies (Weaver, 1998).

Endogenously controlled daily rhythms are generally called circadian rhythms, referring to the fact that the endogenous free-running period of these rhythms is 'about a day' but often slightly deviating from 24 h (Latin: *circa* = about, *dies* = day). As the observations in blind rats by Richter (1967) already suggested, the hypothalamic circadian clock uses light to adjust the endogenous period to exactly 24 h and precisely synchronize the endogenous rhythms to the light-dark cycle in the outside world (Pittendrigh, 1981). The photic information is transmitted from the retina to the SCN via a direct neuronal input, the retinohypothalamic tract (Moore and Lenn, 1972). While other environmental factors may influence circadian rhythmicity, there is a general consensus that in mammals, the daily light-dark cycle is the most important time cue or 'zeitgeber' (ZT) for synchronization of endogenous rhythms to the external environment (Pittendrigh, 1981).

Although much research initially focused on the SCN, it was clear from early on that the hypothalamus does not contain the only clock or

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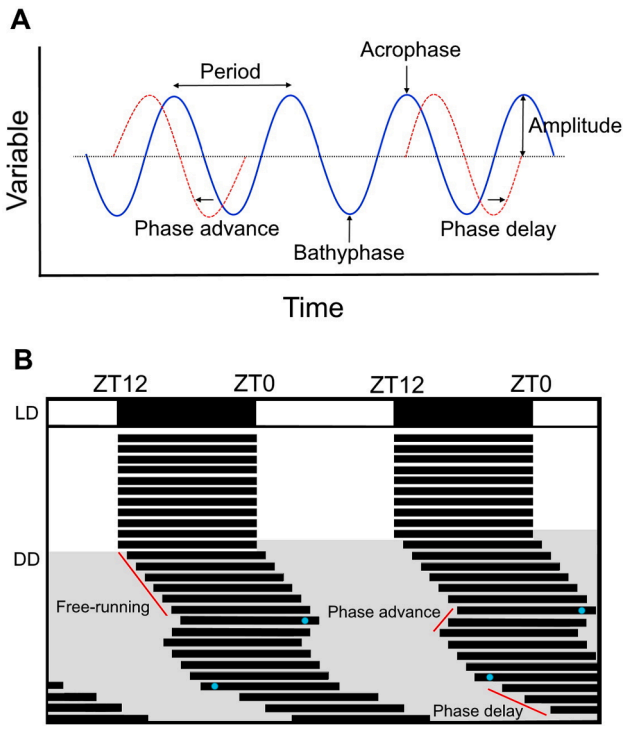

Fig. 1. Circadian rhythm terminology. (A) Representation of a circadian rhythm through time. Period: the duration of one complete oscillation, for example, the time between two consecutive peaks of the rhythm. Amplitude: the difference between the peak or trough (the highest and lowest value of the wave) and the mean value. Phase: the time point of a distinct part of the rhythm or cycle, for example, the peak. Acrophase: time of the peak of the rhythm. Bathyphase: time of the trough of the rhythm. Phase-shift: a shift in the time of a rhythm, advancing or delaying it. (B) A double-plotted actogram, illustrating the activity rhythm of a nocturnal animal. Each horizontal line represents 48 h of the recorded rhythm. The animal was exposed to a light–dark (LD) cycle for the first 11 days (indicated by the white-black bar at the top) and then to constant darkness (DD) the next 16 days (indicated by the grey shaded area in the lower half of the graph). Zeitgeber (German for 'time giver') is an external time cue or stimulus that is capable of entraining or synchronising biological clocks. Zeitgeber time (ZT): unit of time based on the period of a zeitgeber, for example, an external light-dark cycle. In a 12 h:12 h LD cycle, ZT 0 is defined as the time lights go on and ZT 12 as the time lights go off. Free-running: the state of an endogenous biological rhythm when it is not exposed to and affected by external time cues. Light stimuli (blue dots) at certain times of day can phase shift the endogenous rhythms: light during the first half of the subjective night phase delays the rhythm; light during the second half of the subjective night phase advances the rhythm.

oscillator in the body. Studies in the nineteen-sixties and seventies already showed that various organs could exhibit 24 h rhythms *in vitro*, including the adrenal glands (Andrews and Folk, 1964; Ungar, 1964) and liver (Langner and Rensing, 1972; Rensing et al., 1974), suggesting that rhythmicity was intrinsic to these tissues. Currently, the general view is that every organ and tissue, and perhaps every cell, may have its own endogenous oscillatory activity (Balsalobre, 2002; Dibner et al., 2010). Nowadays, rhythmicity in tissues is often assessed by measuring the expression of the so-called clock genes and/or their protein products that together make up the molecular clock machinery, which is auto regulated by negative feedback loops (Fig. 3). Hence, daily or circadian rhythms in the mammalian body are the result of a complex constellation of interacting oscillators. In this growingly complex circadian system, the SCN is considered to be the master clock that fine-tunes the various rhythms among each other and also synchronizes them to the environmental day-night cycle (Dibner et al., 2010; Mohawk et al., 2012; Reppert and Weaver, 2002).

It is not difficult to imagine that disruption of circadian organization and disturbance of precisely tuned rhythmic processes can lead to malfunction and disease (Bass and Lazar, 2016; Roenneberg and Merrow, 2016; Takahashi et al., 2008). This notion is supported by numerous studies on the health consequences of shift work and social jetlag, conditions that represent a mismatch between the endogenous circadian system and the external time (Knutsson, 2003; Roenneberg et al., 2019; Wright et al., 2013). These conditions may also result in disrupted phase relationships among the endogenous rhythms within the body and such a state of internal desynchronization is likely to have an impact on health. Indeed, chronic shift work has been linked to altered sleep and fatigue, development of metabolic and cardiovascular diseases, and increased risk for colon and breast cancer (Haus and Smolensky, 2006; Knutsson, 2003; Reinberg and Ashkenazi, 2008; Wright et al., 2013). Importantly, while the link between shiftwork and disease risk in humans is inevitably complex and multifactorial, experimental studies with animal models have clearly demonstrated that chronic circadian disorganization per se can be a direct causal factor in organ disease and even early death (Martino et al., 2008, Martino and young, 2015).

In the same context of the association between circadian organization and health, it is an important question whether the endogenous circadian system is sensitive to disturbance by stress. Conditions of uncontrollable and chronic stress are triggers for a variety of diseases, many of which are associated with strong alterations in daily rhythms in behavior and physiology (e.g., disturbed sleep-wake rhythm, disturbed rhythms in metabolism and food intake, disturbed neuroendocrine rhythms). One might thus argue that disruption of circadian organization could be one important underlying mechanism of stress-related disorders such as cardiovascular diseases and psychiatric disorders. Therefore, the purpose of this review is to discuss the available literature on the effects of stress and stress hormones on endogenous clocks and circadian rhythms.

2. Stress and stress hormones

One complication that comes with reviewing literature on the consequences of stress is the fact that the concept of stress itself has been subject to debate ever since its introduction by Hans Selye (Selye, 1950; for a critical evaluation see Koolhaas et al., 2011). Stress was originally defined as the non-specific physiological response of the body to any noxious stimulus. Today most people will still largely adhere to this definition and consider stress to be something like an aversive condition or stimulus that results in a bodily response and a state of physiological activation. This physiological activation then supports an adequate behavioral response to deal with the stressful situation at hand (a "fight or flight" reaction). However, while aversive stressful conditions and stimuli are most often associated with physiological activation, one needs to be aware that the reverse is not always true: the physiological activation by itself does not necessarily always indicate a state of stress in the sense of a threatening and potentially harmful condition. The literature clearly shows that the physiological 'stress' response to positive, rewarding stimuli that are generally not considered as stressors can be as large as the response to negative, aversive stimuli (Koolhaas et al., 2011). For example, studies in laboratory rodents demonstrate that sexual stimuli and sexual behavior are accompanied by high plasma levels of glucocorticoid 'stress' hormones (Bonilla-Jaime et al., 2006; Bronson and Desjardins, 1982). In fact, the levels of 'stress' hormones in response to a sexual interaction can be as high as the levels seen after severe social defeat stress (Buwalda et al., 2012). Other spontaneous behaviors such as locomotor activity and feeding are also associated with increased levels of stress hormones (Girard and Garland, 2002; Shiraishi et al., 1984). Clearly, these hormones have well-established metabolic functions and play an important role in the mobilization and distribution of energy and oxygen that goes beyond dealing with unexpected threats or challenges.

In the current review, we discuss the literature on a wide variety of

animal models of stress that are undeniably based on uncontrollable aversive stimuli such as social defeat, immobilization, electrical shocks, etc. Such conditions are most often associated with a strong activation of the two classical neuroendocrine stress systems: the autonomic sympathetic-adrenal-medullary (SAM) system and the hypothalamic-pituitaryadrenal (HPA) axis (Axelrod and Reisine, 1984; Johnson et al., 1992; Ulrich-Lai and Herman, 2009). In addition, we also discuss a variety of studies that directly apply stress hormones because they may provide insights into the mechanism underlying the effects of real life stressors, but it has to be kept in mind that such findings are not exclusive for negative conditions.

Activation of the SAM system increases levels of noradrenaline (mainly from sympathetic nerves) and stimulates the medulla of the adrenal glands to secrete adrenaline, which are involved in the "fight or flight" response (Ulrich-Lai and Herman, 2009). Although peripherally secreted catecholamines are unable to cross the blood-brain barrier to reach the brain, activation of the *locus coeruleus* (LC) leads to secretion of noradrenaline in the brain that parallels adrenal activity (Svensson, 1987).

In the HPA stress response axis, the paraventricular nucleus of the hypothalamus (PVN) produces and releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH stimulates secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland and this action can be amplified by AVP. ACTH is then transported by the blood circulation and reaches the cortex of the adrenal gland where it induces glucocorticoid synthesis and secretion (for review, see Papadimitriou and Priftis, 2009). These hormones participate in metabolic control, cardiovascular activity, and immune responses, among other functions, by binding to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). The latter are activated when glucocorticoid levels are high, such as around the peak of circadian secretion and in stressful situations. Glucocorticoid receptors are also involved in the negative feedback regulation of the HPA axis to return to basal activity levels upon cessation of stress (de Kloet, 2014). Glucocorticoid receptors are widely distributed in the body and upon activation they can stimulate or inhibit the transcription of many genes, including clock genes, by binding to glucocorticoid responsive elements (GRE) in the promoter region (Yamamoto et al., 2005).

3. Potential stress input pathways to the SCN

One way to address the question of whether the master clock in the SCN might be sensitive to stress is to determine whether it expresses receptors for classical stress signals from the HPA axis and the sympathetic nervous system.

Glucocorticoid receptors have been detected in the SCN of infant rats, at postnatal days 2 and 8, but they are less present at postnatal days 12 and 16 and are no longer observed by postnatal day 20 and in adult rats (Rosenfeld et al., 1988). The CRH receptor 1 (CRH-R1) is expressed in the SCN, which might suggest a (reciprocal) connection with the PVN (Campbell et al., 2003). However, retrograde tracing markers did not reveal PVN inputs to the pacemaker in rats (Moga and Moore, 1997) and neither CRH cells nor fibers were found in the area bordering the SCN in ground squirrels (Reuss et al., 1989). It is, therefore, uncertain whether the SCN is indeed sensitive to CRH input and, if so, where this input would be coming from.

With regards to the sympathetic nervous system, Legoratti-Sánchez et al. (1989) identified a possible bidirectional communication between the SCN and the noradrenergic LC in rats by recording evoked potential in one region after stimulation of the other (and *vice-versa*). When the SCN or the LC was electrolytically lesioned, the evoked potentials were no longer observed after stimulation of one of the areas. However, there is no histological evidence for a direct SCN-LC connection, suggesting the existence of a multi-synaptic pathway (Legoratti-Sánchez et al., 1989). On the other hand, α1- and α2-adrenoreceptors are found in the rat SCN, as shown by prazosin and *para*-aminoclonidine binding in autoradiograms (Morien et al., 1999), which may explain findings of catecholamine modulation of clock gene expression (Terazono et al., 2003). While these studies together suggest the existence of a potential input from the sympathetic nervous system to the master clock in the SCN, it is uncertain whether activation of this pathway occurs under conditions of stress and how that potentially would affect the activity of the SCN.

Two additional inputs to the SCN that might be relevant in the

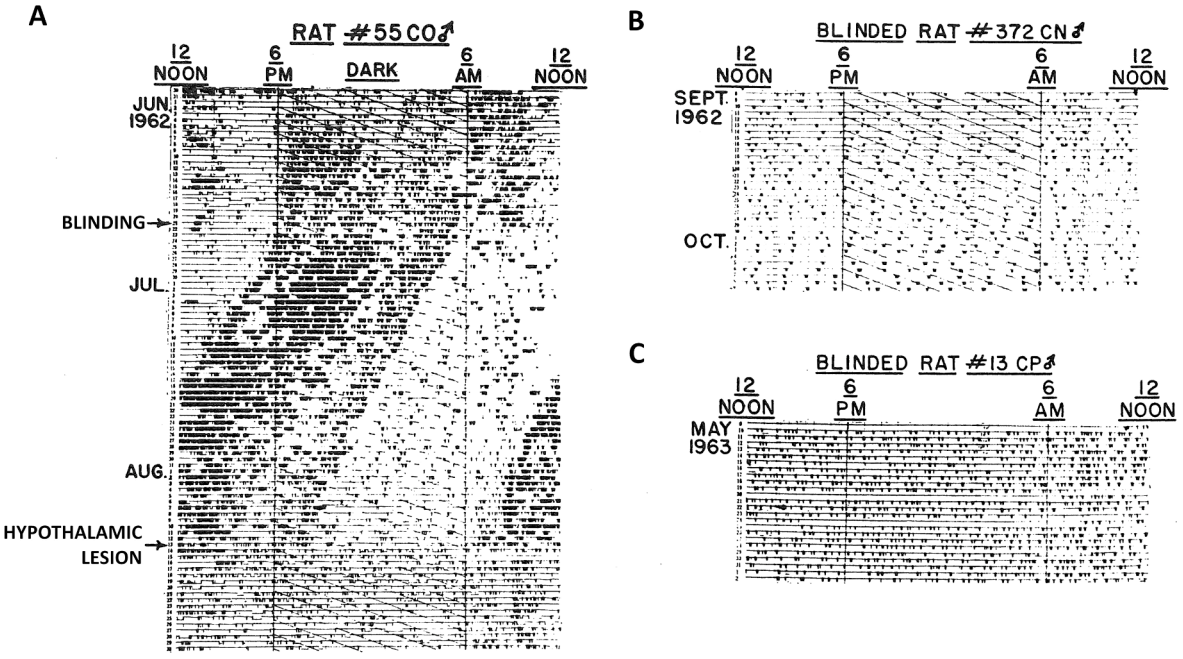

Fig. 2. Effects of blinding and hypothalamic lesion on the activity patterns of rats. (A) Running activity of a rat initially showing a rhythm that was synchronized to a 12 h:12 h LD cycle. After blinding, the animal displays a free-running rhythm with a period shorter than 24 h. After hypothalamic lesion the animal becomes arrhythmic, with activity evenly distributed across the 24 h cycle. (B) Eating activity of a rat after hypothalamic lesion. (C) Drinking activity of a rat after hypothalamic lesion (C). Adapted from Richter (1967).

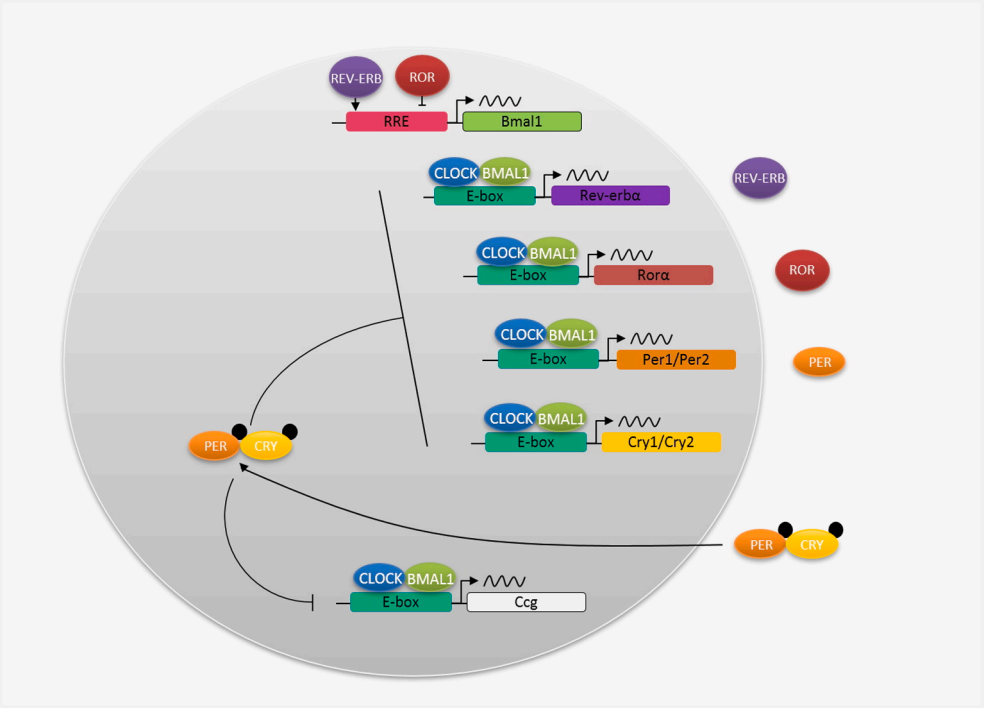

Fig. 3. Molecular circadian clock machinery consisting of an autoregulatory feedback loop. The transcription factors CLOCK and BMAL1 activate the transcription of *Per1, Per2, Cry1, Cry2, Rev-erbα, Rorα* and clock-controlled genes (Ccg). In the core feedback loop, PER and CRY proteins form complexes that inhibit the activity of CLOCK and BMAL1. In a second feedback loop, REV and ROR compete for binding to Bmal1 promoter region and inhibit or activate transcription. Adapted from Mohawk et al. (2012).

context of stress originate from the median raphe (serotonin) and the intergeniculate nucleus (neuropeptide Y). In addition, the intergeniculate leaflet receives innervation from the dorsal raphe nucleus, providing another indirect raphe-SCN connection (Morin, 2013). Both the raphe nuclei and the intergeniculate leaflet are responsive to a variety of stimuli, including stressors (Webb et al., 2008, 2010). However, while these serotonergic and neuropeptide Y inputs to the SCN can clearly modulate the phase of the master clock, it remains uncertain whether this is truly an effect of stress or a consequence of non-specific arousal (for further discussion on this issue, see Section 6).

4. Stress effects within the SCN

Another way of addressing the question of stress input to the circadian master clock is by assessing changes in gene expression within the SCN in response to stimuli that might be classified as stressful. Enhanced expression of the immediate early gene c-fos is often used as an indication of neuronal activity, which may occur after any kind of stimulus, including stress. In one study, c-fos expression was observed in the SCN after intraperitoneal (IP) saline injection in rats (Edelstein and Amir, 1995), but another study did not show the same in hamsters (Mead et al., 1992). Likewise, c-fos levels in the SCN were increased in rats after 2 h of immobilization but not after movement restraint stress (Briski and Gillen, 2001; Edelstein and Amir, 1995). Together, these findings do not make a strong case for a general effect of stress or stress hormones on the master clock. At best, they suggest that c-fos expression in the SCN is affected by specific stimuli or conditions.

A number of studies have assessed effects of certain stressors on core clock genes and proteins in the SCN, particularly the levels of Period 1 and Period 2 (*Per*1 and *Per2* mRNA or PER1 and PER2 proteins). Rats exposed acutely to 30 min of restraint or 15 min of forced swimming at different times of the day (ZT 3, ZT 5 and ZT 8) did not exhibit PER1 alterations in the SCN (Al-Safadi et al., 2014). In mice subjected to 18 days of repeated social defeat stress during the dark phase, the amplitude of the PER2 rhythm was increased (Bartlang et al., 2014). However, after 4 weeks of chronic unpredictable stress or 7 days of 3 h restraint stress at ZT 6, the amplitude of PER2 expression was found to be reduced (Jiang et al., 2011; Kinoshita et al., 2012, respectively). Also, after 7 days of predator-scent stress, *Per*1 and *Per2* mRNA expression were increased at ZT 19 and decreased at ZT 13 (Koresh et al., 2012). Therefore, it appears that chronic stress can modulate the amplitude of clock gene expression in the SCN in a time-dependent fashion. In contrast to these amplitude effects, the phase and period of PER2 expression in the SCN do not seem to be affected by restraint stress (Tahara et al., 2015) or by repeated social stress (Ota et al., 2020; Tahara et al., 2015). These latter studies made use of PER2::LUCIFERASE (PER2::LUC) knock-in mice in which the firefly luciferase gene is coupled to the clock gene Per2. The resulting PER2::LUC fusion protein can serve as a reporter of rhythmic PER2 expression in different tissues (Yoo et al., 2004). When tissues are collected and cultured in a medium containing luciferin, the luciferase enzyme catalyzes the breakdown of the luciferin to produce a bioluminescent signal that corresponds to the levels of PER2. When PER2::LUC mice were restrained on 3 consecutive days at different times (ZT 0-2, ZT 4-6 or ZT 12-14), there was no phase difference between PER2 expression in SCN slices from stressed and control animals (Tahara et al., 2015). Similarly, when PER2::LUC mice were submitted to social defeat stress during the second half of the active phase on 10 consecutive days and had the SCN collected 1 h after the last defeat, there were no phase or period changes in PER2 expression compared to control mice (Ota et al., 2020). Moreover, when the SCN of stress naïve mice was cultured with corticosterone, the phase and period of the PER2 rhythm were not different from the ones without corticosterone, suggesting that in terms of period and phase the master clock is protected against the effects of stress (Ota et al., 2020). The latter finding is of course in line with the fact that the adult SCN does not express receptors for glucocorticoids (Rosenfeld et al., 1988).

Other studies have evaluated whether stress signals can reach the SCN by observing possible alterations in the production and release of specific neurotransmitters. For example, vasopressin (AVP) synthesized and released by neurons of the dorsomedial part of the SCN was increased after 10 min of forced swimming or active shock avoidance training (Engelmann et al., 1998; Biemans et al., 2003, respectively). After one session of scrambled footshock in rats, AVP mRNA was enhanced in the SCN, but vasoactive intestinal peptide (VIP) mRNA produced by neurons in the ventromedial region of the SCN was decreased (Handa et al., 2007). Furthermore, in adrenalectomized

(ADX) rats, chronic administration of corticosterone by means of a subcutaneous pellet enhanced AVP mRNA expression at ZT 5, while it elevated VIP mRNA at different times, abolishing its rhythm in the SCN. These results suggest that glucocorticoids may influence the expression of two main neuropeptides in the SCN by different mechanisms, since glucocorticoid administration resulted in different changes for AVP and VIP gene expression (Larsen et al., 1994). However, since the adult SCN does not express glucocorticoid receptors (Rosenfeld et al., 1988), this effect is thought to be mediated by other systems influenced by glucocorticoid levels, which then send inputs to the SCN, such as the medial preoptic nucleus, paraventricular thalamic nucleus, ventromedial and dorsomedial hypothalamic nuclei (Krout et al., 2002).

Together these findings do not yet provide a clear picture of how stress in general may affect the SCN. While the period and phase of the master clock in most cases is unaltered, certain stressors may affect other aspects of the clock machinery (amplitude of PER rhythms, vasopressin release), but the functional consequences of these changes remain largely unknown.

5. Stress effects on rhythms: Changes in clocks or masking?

As will be discussed in the next sections, changes in physiological and behavioral rhythms following some forms of stress have been reported in numerous studies. However, one important issue to keep in mind is that changes in the shape of a rhythm do not necessarily reflect changes in the circadian oscillatory mechanism involved in regulating these rhythms. It may very well be that the underlying endogenous oscillators or clocks are unaffected and only their output is masked by alterations elsewhere in the brain or body (Mrosovsky, 1999; Rietveld et al., 1993). The shape of the body temperature rhythm, for instance, can be modified by a variety of exogenous and endogenous factors independent of the circadian system including ambient temperature, meals and food digestion, physical activity and sleep, etc. (Hiddinga et al., 1997). Going for an early morning run and having a warm shower afterwards will have major effects on the body temperature profile, but this is unrelated to the circadian clock system regulating the basal rhythm in temperature. More relevant to the context of this review, experiencing stress often induces an acute increase in body temperature and sometimes even long-lasting changes in the temperature rhythm, but such changes may not indicate an altered circadian regulation of this rhythm (see Fig. 4) (Meerlo et al., 1997, 2002). Clearly, the shape and amplitude of most rhythms are not exclusively determined by the circadian system and the rhythms that are measured, most often, reflect a combination of circadian and non-circadian processes. Therefore, to be able to draw conclusions on whether or not differences in the shape of a rhythm are truly related to changes in circadian organization, one has to study features that are characteristic and specific of the endogenous oscillators. For example, maintaining organisms under constant conditions, also called 'free-running' conditions, when intrinsic circadian characteristics such as the period and phase can be measured. Nowadays, another procedure to directly probe circadian function is to assess the expression of clock genes and proteins in different organs and tissues.

6. Stress-induced changes in rhythms: Stress or arousal?

An important consideration with respect to effects of stress is the fact that arousal is a concept that may partly overlap with stress but is not necessarily the same thing. This is important because studies in laboratory rodents, particularly hamsters, have reported pronounced alterations in circadian function in response to arousing stimuli that induce locomotor activity (Mrosovsky, 1996). These circadian effects of arousal may sometimes erroneously be interpreted as effects of stress, especially when the stimulus or condition inducing the arousal appears to be aversive at a first glance. Good examples of this are the studies in hamsters describing how circadian rhythmicity is affected by social

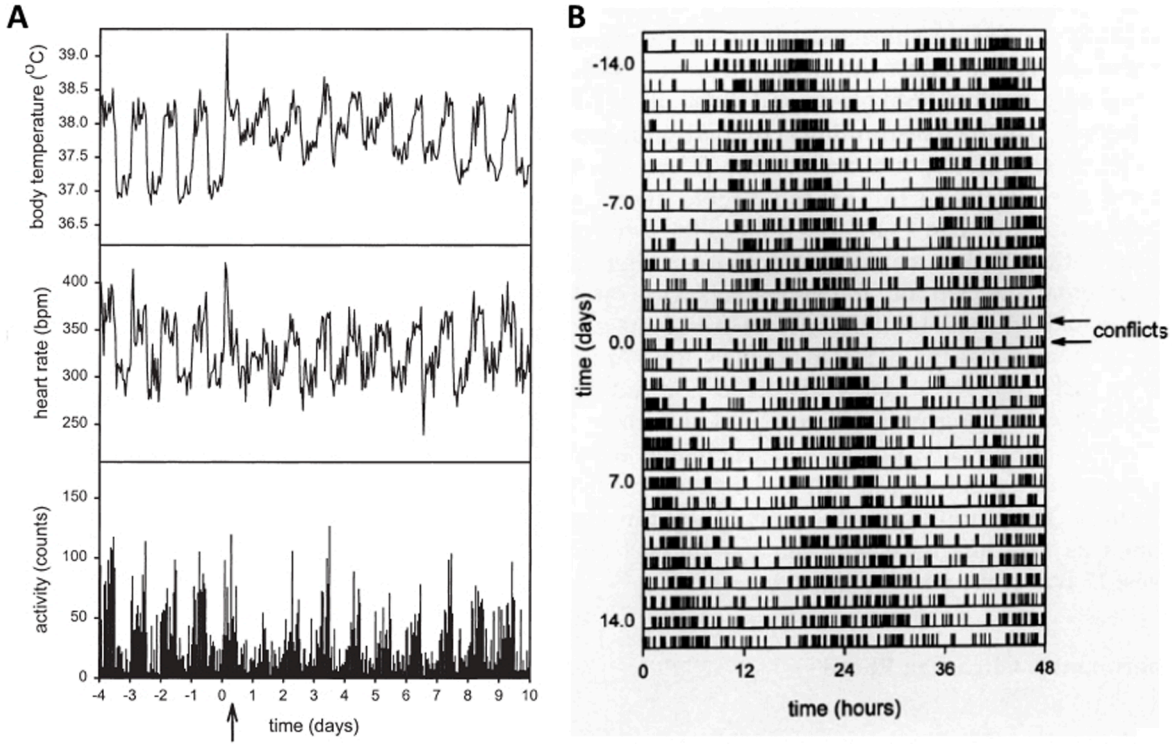

Fig. 4. Effects of social defeat stress on circadian rhythms in rats. (A) Example of changes in daily rhythms of body temperature, heart rate and locomotor activity of an individual rat after a single social defeat stress (arrow day 0). Defeat stress reduces the amplitude of the rhythms, an effect that gradually normalizes in the week thereafter. (B) Double-plotted actogram of an individual rat under constant conditions. Social defeat stress on two consecutive days (arrows on the right) temporarily suppresses activity but does not affect the phase or free-running period of the rhythm. For details, see Meerlo et al. (2002) (A) and Meerlo et al. (1997) (B).

conflicts. In some of these studies, male hamsters were placed together for 30 min, unless serious aggression occurred, in which case the animals were separated as soon as fighting erupted (Mrosovsky, 1988; Refinetti et al., 1992). Although actual fighting was prevented in most cases, the strong tendency for aggression suggests that the interaction may have been perceived as stressful. Interestingly, these social interactions lead to a pronounced shift of the circadian activity rhythm in one study (Mrosovsky, 1988) but not in the other (Refinetti et al., 1992). In the first study, most hamsters displayed a period of intense wheel running upon return to the home cage, indicating a high level of arousal; in the second study, however, the animals did not run consistently in the wheel. From other studies in hamsters, it is known that wheel running is a potent modulator of the circadian organization and can result in pronounce phase shifts (Mrosovsky, 1996). Hence, it seems that it is not the potentially adverse and stressful social conflict itself that resulted in a shift in circadian rhythms but, instead, the arousal associated with wheel running afterwards. Even though wheel running may be associated with physiological activation and release of classical stress hormones, it is not a cognitive stressor in the sense of being an uncontrollable and unpredictable adverse condition (Koolhaas et al., 2011). Quite the opposite, hamsters chose to run in the wheel most likely because it is rewarding and, if anything, a positive experience (Novak et al., 2012).

In another series of studies in Syrian hamsters, Mistlberger and co-workers compared phase shifting effects of various arousal procedures, and showed that phase shifts did not correlate with the level of stress as defined by the release of corticosterone (Mistlberger et al., 2003). For example, restraint stress for 3 h during daytime did not induce phase shifts. However, 3 h of social stress (an intense psychological stress) or exposure to an open field (a mild stress) resulted in large phase shifts that correlated with indexes of forward locomotion. The latter led the authors to conclude that phase shifts associated with arousal in the usual sleep period are not related to stress per se, but are dependent on the expression of at least low levels of locomotor activity (Mistlberger et al., 2003).

Additional evidence that activity affects the clock comes from a report on blind female rats displaying shorter free-running period when given access to running wheel (Yamada et al., 1988); the same effect being observed in male mice when the activity is concentrated in the beginning of the subjective dark phase, whereas the period is increased when the activity is concentrated at the end of the subjective dark phase (Edgar et al., 1991).

7. Stress does not affect period and phase of output rhythms controlled by the SCN

The pioneering studies of Curt Richter in the 1960s are not only of general interest to the field of chronobiology but are also of particular interest for this review on stress. Richter's attempts to unravel the mechanisms and conditions controlling and modulating endogenous circadian rhythms included a wide range of manipulations that can safely be considered as severe stressors (Richter, 1967). For example, he subjected rats to forced swimming, restraint and electric shocks, often repeatedly and for several days. The experiments were usually done under constant conditions to assess whether these stressors would affect free-running endogenous circadian rhythmicity. The prolonged exposure to severe stress resulted in strong suppression of activity and in some cases, rhythmicity was hardly visible. Yet, upon cessation of the stress exposure, activity would gradually normalize and resume, more or less, at the expected time, indicating that the period and phase of the endogenous clock driving the activity rhythm had not been affected (Richter, 1967). It appeared that this clock kept ticking at the same pace throughout the stress days and only its output had been temporarily masked. One may argue that the methods and analyses Richter used in those days were not highly sophisticated; yet, later studies with different approaches and more detailed analyses largely confirmed his conclusions.

Several studies in rats have shown that social conflicts and defeat by an aggressive conspecific result in severe disruption of daily rhythms in locomotor activity, heart rate and body temperature (Meerlo et al., 1996, 1999; Tornatzky and Miczek, 1993; also see Fig. 4). Although repeated exposure results in more pronounced rhythm changes, even a single social defeat stress leads to disrupted rhythmicity lasting for days up to weeks after the actual social interaction (Meerlo et al., 1996, 1999). There is some evidence that the most pronounced changes in rhythm occur in animals that do not counter attack in a fight, in line with the view that the stress experience and its subsequent consequences are determined by the perception of uncontrollability (Meerlo et al., 1999). A number of studies specifically addressed the question of whether the changes in activity and body temperature rhythms resulting from uncontrollable social stress were a consequence of alterations in the endogenous circadian timing system. In one experiment, rats were subjected to social defeat stress in the first half of the activity phase (Meerlo et al., 1997), whereas in another, social defeat took place in the middle of the resting phase (Meerlo and Daan, 1998). Neither study found an effect of stress on phase or period of the free running rhythms under constant conditions (Meerlo et al., 1997; Meerlo and Daan, 1998). In line with Richter's earlier conclusions, these findings suggest that severe social stress does not affect the endogenous circadian clock driving activity and temperature rhythms. Although its output may become masked by stress-induced disturbances elsewhere in the body, the central pacemaker in the SCN appears to be unaffected.

One might think that a single episode of stress is not sufficient to affect the pacemaker in the SCN; yet, investigations with repeated and more chronic social stress have produced largely similar results. Phase and period of free-running activity rhythms were not affected when mice were repeatedly exposed to social defeat stress during the active or the resting phase over the course of 10 days (Ota et al., 2018), which is in line with the finding that there is no change in phase and period of PER2 expression in the SCN (Ota et al., 2020). Similarly, other studies showed no significant change in the free-running period of the activity and body temperature rhythms after a 14 days of social defeat stress during the active phase / dark phase in C57BL6/J mice, although a small period effect was observed in C57BL6/N mice (Bartlang et al., 2015).

In mice subjected to a protocol of chronic intermittent stress that included pair housing with unfamiliar males, forced swimming, and movement restraint, activity was temporarily suppressed, but the free-running period of the activity rhythm under continuous darkness was unaffected (Solberg et al., 1999). Also, the effect of 30-min daily immobilization stress on free-running activity rhythms in rats under constant conditions was investigated over a 93-day interval and compared with the milder 30-min sessions of novelty exposure or brief handling. Although in each group 20 to 30% of the rats showed mild changes in circadian period in the course of the experiment, there were no significant differences between the groups (Barrington et al., 1993). Therefore, this study does not support the hypothesis of changes in the master clock driving the activity rhythm, even with repeated stress exposure over a period of several months.

8. Stress effects on peripheral oscillators

The data presented thus far suggest that the circadian master clock in the SCN is rather well protected against disturbance by stressful stimuli. An important remaining question is whether stress or stress hormones can affect other clocks or oscillators that are known to reside in tissues throughout the body, which are normally under regulation of the central pacemaker in the SCN (Balsalobre, 2002; Dibner et al., 2010).

One study in mice showed that restraint stress for 1 h enhanced *Per1* mRNA in liver, heart, lung and stomach without alteration in other clock genes (Yamamoto et al., 2005). In another study in mice, restraint stress on 5 consecutive days disrupted the circadian expression of PER2 by decreasing its amplitude and phase shifting the peak of expression in the

bladder (Ihara et al., 2019). A daily session of restraint stress during the daytime for 3 days/week and 4 weeks in total, which did not affect the PER2 rhythm in the master clock in the SCN, caused a major phase advance of several hours in the PER2 rhythm in liver, kidney, and submandibular gland (Tahara et al., 2015; see Fig. 5). In fact, the phase advance was particularly large after 1 week of stress and had somewhat diminished after 4 weeks of stress, particularly in the liver, suggesting a habituation to the repeated restraint. In agreement with this idea, plasma corticosterone responses to stress were reduced after 4 weeks compared to the responses in the first week. Importantly, further experiments showed that shifts of the PER2 rhythm where dependent on the time of day of stress exposure, with phase advances following stress during the light phase, no phase changes following stress in the early dark phase, and phase delays following stress in the late dark phase (Tahara et al., 2015). The same study showed that these effects were not restricted to restraint stress since comparable phase advances in clock gene rhythms in liver, kidney and submandibular gland were found when mice were exposed to repeated social defeat stress (Tahara et al., 2015). In one of our own studies with PER2::LUC mice, we confirmed this latter finding and showed that the PER2 rhythm in the liver was delayed by about 8 h following 10 days with social defeat stress during the second half of the activity phase (Ota et al., 2020). Also, chronic subordination stress for 14 days with physical interactions during the early light phase resulted in a phase advance of the PER2 rhythm of about 2 h in the adrenal gland and about 1 h in the pituitary gland (Razzoli et al., 2014). Interestingly, a single defeat plus 8 h of sensory contact induced an advance of the PER2 peak phase only in the adrenal but not in the pituitary gland. These findings indicate that peripheral clocks in different tissues may vary in their sensitivity to stress input and phase changes may depend on the duration of stress exposure. In this particular case, defeat stress first affected the more sensitive adrenal clock, whereas chronic stress also shifted the pituitary clock (Razzoli et al., 2014).

Although few studies have specifically addressed this issue, there is evidence that effects of stress on peripheral clocks may be sex dependent. Repeated restraint during the light phase for 7 days in PER2::LUC mice reduced the amplitude, advanced the phase and lengthened period of adrenal PER2 rhythms, but it did so in a sexually dimorphic manner (Stagl et al., 2018). Overall, the effects on amplitude and phase were larger in male mice but the changes in period were more persistent in females. Further studies are needed to assess whether sex-dependent effects of stress on circadian oscillators may vary for different tissues and perhaps also depend on the nature of the stressor.

The mechanism through which different stressors affect peripheral clocks is not fully understood but indirect evidence suggests that it may involve the SAM and HPA axes. The seminal study by Tahara and colleagues, in addition to reporting on the effects of restraint and social defeat stress, further showed that repeated injections of noradrenaline, adrenaline or the synthetic glucocorticoid dexamethasone produced similar phase changes in the PER2 rhythm in liver, kidney and submandibular gland (Tahara et al., 2015). Moreover, liver tissue of PER2::LUC mice cultured in medium with corticosterone resulted in a phase delayed PER2 rhythm similar to what was reported for social defeat stress in the late active phase (Ota et al., 2020). Also, injections with dexamethasone altered rhythmic clock gene expression in liver, kidney, and heart, but not in the SCN (Balsalobre et al., 2000). Likewise, adrenaline injections *in vivo* or dissolved adrenaline *in vitro* increased*Per1* expression in the liver (Terazono et al., 2003) and a

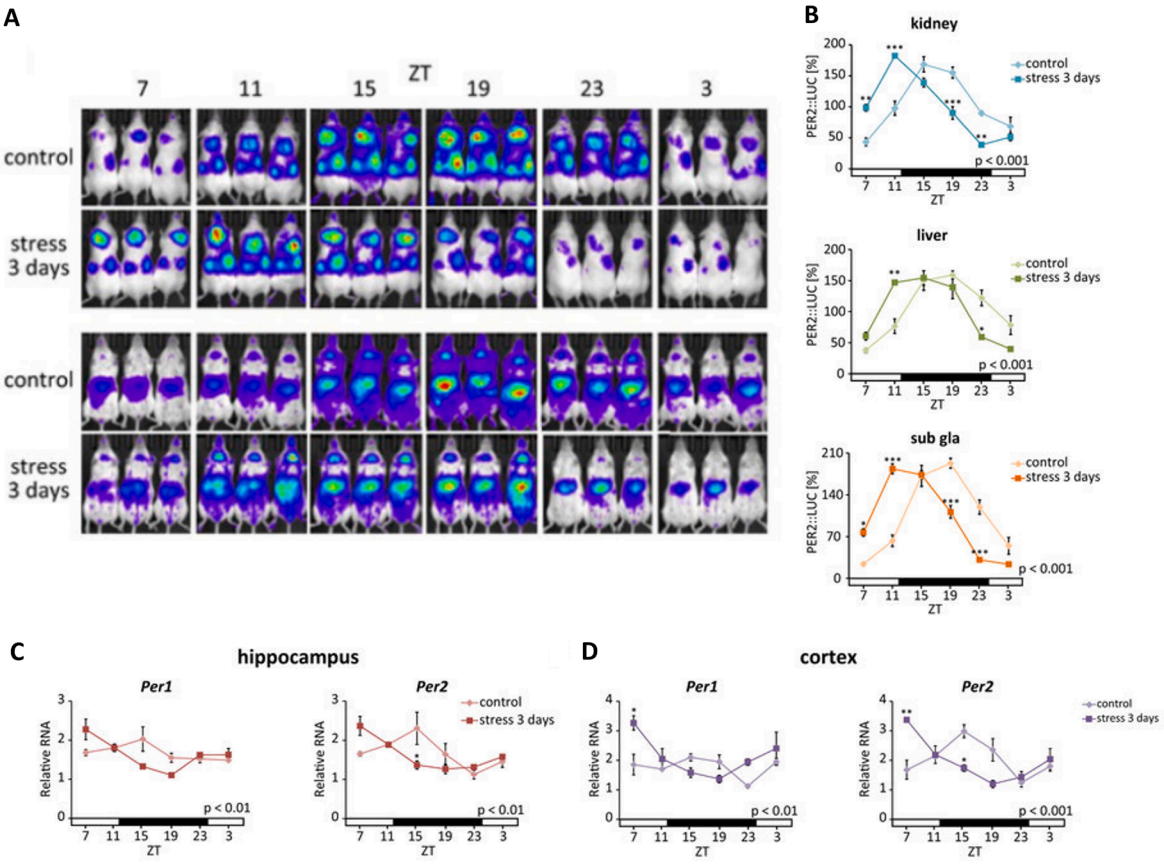

Fig. 5. Effects of 3 days of restraint stress at ZT 4–6 on PER2 rhythms in peripheral tissues. (A) Representative images of *in vivo* PER2::LUC bioluminescence signals at different times of day (ZT 7, 11, 15, 19, 23 and 3) in 2 control mice and 2 stressed mice. (B) Repeated restraint stress at ZT 4–6 phase advanced the PER2::LUC rhythms in kidney, liver and the submandibular gland (sub gla). (C and D) Repeated restraint stress phase advanced expression of Per1 and Per2 mRNA in hippocampus and cortex. Adapted from Tahara et al. (2015).

combination of adrenaline and noradrenaline phase shifted the expression of *Per1* and its regulating transcription factors genes *E4bp4* (E4 promoter-binding protein) and *Dbp* (D-box binding protein), in aortic cells *in vitro* (Reilly et al., 2008). While together these results show that catecholamines and glucocorticoids to some degree mimic the effects of real stressors on peripheral clocks, further studies are needed to experimentally assess the involvement of the HPA axis and SAM system, e.g., by blocking these pathways in animals exposed to stress.

In addition to the classical neuroendocrine stress factors, an alternative mechanism through which stress might affect peripheral oscillators is by inducing changes in body temperature. As discussed in previous sections, it is well-established that uncontrollable stressors such as social defeat cause acute increases in body temperature as well as long lasting changes in the daily temperature rhythm (e.g., Meerlo et al., 1996, 1997, 1999; see Fig. 4). *In vitro* experiments suggest that temperature may be a resetting signal for peripheral oscillators, as demonstrated by heat pulses of 1 h or 6 h from 36 °C to 38 °C in pituitary and lung tissues (Buhr et al., 2010). By simulating body temperature fluctuations (36–38.5 °C) in mouse *ex vivo* cultures, researchers showed that physiological body temperature oscillations are capable of entraining and enhancing the amplitude of the circadian rhythms of peripheral clocks (Buhr et al., 2010; Brown et al., 2002). The expression of genes encoding for heat shock proteins or heat shock factors (HSFs) and cold-inducible RNA-binding proteins (CIRPs) are temperature-dependent, which may provide a link between temperature and peripheral clock resetting (Schibler et al., 2015). Whereas HSF1 is involved in the phase resetting of circadian clocks, CIRPs mainly influence the amplitude of circadian gene expression by modulation of the CLOCK and BMAL1 accumulation (Morf et al., 2012; Schibler et al., 2015). Since most studies on temperature and circadian clocks are either in isolated cells or in ectothermic animals, such as drosophila and zebrafish, additional *in vivo* experiments in mammals are needed to assess whether these temperature-dependent factors play a role in stress effects on peripheral clocks.

Finally, stress may alter behavior and feeding times, which in turn could affect the timing of peripheral clocks (Mistlberger and Antle 2011). Indeed, it has been demonstrated in rodents that timed feeding during the day can change the phase of circadian gene expression in peripheral tissues such as the liver, lung, kidney, heart and pancreas (Damiola et al., 2000; Stokkan et al., 2001). Ultimately, the mechanism through which stress-induced changes in meal timing could affect peripheral clocks may involve all of the mechanism mentioned above, that is, the release of endocrine factors such as glucocorticoids and/or increases in core temperature associate with processing of food.

Taken together, a gradually increasing body of work suggests that at least certain stressors can affect and shift peripheral oscillators, temporarily altering their phase relationship with the master clock in the SCN and the external light dark-cycle. Such effects of stress appear to be time-of-day dependent, tissue dependent and sex dependent. Potential mechanisms underlying these stress effects may include the HPA and SAM axes, although other stress-associated processes such as increased body temperature and changes in meal timing may be involved as well. Whether such changes in circadian organization represent a functional adaption to deal with the stressor or a maladaptive state of internal desynchronization that may contribute to stress-related disorders remains to be seen (see Section 10).

9. Neonatal perspectives

The data discussed so far were largely based on studies in adult laboratory rodents. One of the reasons the master clock in the SCN is largely unresponsive to stress may be the fact that in adulthood it does not express glucocorticoid receptors. However, since these receptors are still present in the SCN during the early perinatal phase (Rosenfeld et al., 1988), this raises the question whether stress during early life might perturb the SCN and affect the developing circadian system. This could happen directly by stress experienced in the offspring or indirectly by stress in the mother that is transmitted to the offspring by, for example, glucocorticoids through the placenta or the milk (Astiz and Oster, 2018; Maccari et al., 2003; Weinstock, 2005).

The circadian system develops gradually and in laboratory rats the SCN already appears between embryonic days 14 and 17, but maturation occurs until postnatal day 10. Synchronization of the developing circadian system to the external light-dark cycle already takes place in utero by maternal cues, although it is not yet fully clear whether this is by maternal feeding, temperature, hormones or a combination of all these factors (Hastings et al., 1998; Sumova et al., 2012). Daily rhythmicity in activity of pups can be observed from around postnatal day 9 or 10 (Smith and Anderson, 1984). Around the same time, the retinal innervation to the SCN is functional, although the eyes only open some days later (Sumova et al., 2012). Until the pups' SCN is mature and responsive to external cycles, maternal interaction is important to keep their rhythms synchronized (Christ et al., 2012; Ohta et al., 2003).

In pregnant animals, the basal level of glucocorticoids in the blood varies across the day, but concentrations in the embryos remain stable due to the enzymatic activity in the placental barrier. However, in stressful situations, excessive glucocorticoid concentrations may reach the embryos and thus interfere with their development (Astiz and Oster, 2018; Maccari et al., 2003; Weinstock, 2005). Indeed, administration of dexamethasone during pregnancy decreased the expression of c-fos in the fetal SCN, suggesting it is sensitive to glucocorticoids (Čečmanová et al., 2019). Also, when dexamethasone was administered to embryonic tissue *in vitro* it caused a phase shift according to the time of treatment and also slowed the oscillation dampening (Čečmanová et al., 2019).

Chronic restraint stress in pregnant mice had prolonged effects on the offspring's SCN, attenuating PER1 expression amplitude and causing more variability in peaks of PER1 expression in individual SCN cells, suggesting that prenatal stress may result in a persistent disturbance in the synchronization among SCN neurons (Yun et al., 2020).

Moreover, it was shown that exposure of female mice to chronic unpredictable stress during pregnancy can lead to persistent changes in circadian behavior in the offspring. Such prenatally-stressed offspring not only displayed changes in their activity patterns but also had altered circadian responses to light. Particularly, when they were exposed to light in the early subjective night, prenatally-stressed mice displayed smaller phase shifts of their activity rhythm, but when they were exposed to light in the late subjective night, larger phase shifts were observed compared to control animals (Kiryanova et al., 2017). Also, studies on maternal movement restriction in rats showed that offspring in adulthood displayed a phase advanced corticosterone rhythm and altered sleep-wake regulation, which included more fragmented sleep, decreased deep slow-wave sleep, and increased REM sleep (Dugovic et al., 1999; Koehl et al., 1997).

Interestingly, the outcome of prenatal stress exposure may to some degree be sex-dependent. In rats, prenatal stress from embryonic day 11 until delivery resulted in phase advanced and increased wheel running activity in males, while it reduced and fragmented activity in females at 4 months of age. When subjected to a 6-h advance shift of the LD cycle, animals exposed to prenatal stressed required more time to resynchronize to the new LD cycle and this effect was larger in female rats (Morley-Fletcher et al., 2019).

Further studies are required to establish how such neonatal stress-induced changes in sleep and circadian rhythmicity in the long run affect performance, wellbeing and health in the offspring.

10. Conclusions and discussion

The circadian system has evolved as an adaptation to the regular and predictable changes in the environment that are the consequence of the Earths' rotation around its axis. These environmental changes consist of the highly regular alternation of day and night, and often in close association with those daily rhythms in ambient temperature and food

availability or accessibility. Endogenously regulated circadian rhythms allow for an optimal temporal organization of behavior and physiology in relation to this cyclic environment. It allows animals to live in synchrony with their cyclic surroundings, and to anticipate and prepare for changes that occur in a predictable daily fashion (Moore-Ede, 1986; Yerushalmi and Green, 2009).

In contrast to the circadian system, the body's stress response systems are an adaptation to the fact that animals are not only exposed to regular and predictable changes in their environment but often have to deal with unexpected threats and challenges (e.g., competitors, predators). In the face of such challenges, a rapid activation of the autonomic SAM system and the HPA axis, in a complex interplay with various other neuroendocrine systems, allows for acute and adequate response to deal with the unexpected situation at hand (Axelrod and Reisine, 1984; Johnson et al., 1992; Ulrich-Lai and Herman, 2009). Whereas the circadian system is an adaptation to predictable aspects of the environment, the stress systems are an adaptation to unpredictable aspects of the environment (Meerlo et al. 2002).

From this functional perspective, it makes sense that the circadian timing system would be thoroughly buffered against effects of unpredictable and uncontrollable stressors that, in many cases, do not contain temporal information relevant for the regulation of daily rhythmicity (Meerlo et al., 2002). In fact, Curt Richter's early studies on rats led him to conclude that the endogenous clock was quite independent from anything that happened in the body (Richter, 1967). More recent work has clearly indicated that his view does not fully hold and that, for example, physical activity or some state of arousal associated with activity provides feedback to the circadian system and is capable of phase shifting the endogenous rhythms (Mrosovsky, 1996). Yet, when it comes to stress, much of the available data from properly controlled and experimental studies in laboratory rodents still suggest that the master clock in the SCN is not disturbed by even severe uncontrollable stressors. While the rhythmic output of the SCN can be masked by stress-induced changes in physiology and behavior elsewhere in the brain or body, the period and phase of the master clock itself remains unaltered, perhaps allowing the body rhythms to return to their normal phases when the stressor has disappeared (Fig. 6; Meerlo et al.,1997, Ota et al., 2018, 2020).

However, an increasing number of studies in laboratory rodents indicate that, in contrast to the master clock in the SCN, circadian clocks elsewhere in the body can be affected by stressors such as restraint and social defeat in a major way, with some papers reporting phase shifts of 6–8 h (Fig. 6; Ota et al., 2020; Tahara et al., 2015). The reported effects of stress on peripheral clocks include a variety of different tissues and organs, including liver, kidney, heart, lungs, adrenals, pituitary and others. Importantly, the magnitude of stress effects is not only tissue dependent but also time-of day dependent, with phase advances often reported following stress exposure in the light phase (i.e., the resting phase in nocturnal rodents) and phase delays following stress exposure in the late dark phase (i.e., the activity phase in nocturnal rodents).

Much work needs to be done to unravel the physiological and molecular mechanisms underlying the effects of stress on peripheral clocks, but available data suggest that they may involve the classical neuroendocrine stress systems, i.e., the SAM system (adrenaline, noradrenaline) and the HPA axis (glucocorticoids). Other stress-induced physiological processes that deserve attention in this respect are, for example, changes in body temperature.

Another important issue for future research is to assess if and/or how effects of stress on circadian organization differ between the sexes. Most studies in this context were done in male rodents, few studies were done in females, and even fewer directly compared the two sexes. Nonetheless, the limited data available indeed suggest that at least the magnitude and persistency of circadian changes following stress may differ between the sexes (Stagl et al., 2018). Furthermore, it will be important to also study female subjects during pregnancy and lactation since stress factors and stress effects may be transmitted to the developing offspring through the placenta or via the milk. This is particularly important since the neonatal SCN, in contrast to the adult master clock, still expresses glucocorticoid receptors, which might make the developing circadian system sensitive to stress in ways not seen in adulthood.

Finally, one of the main challenges for future research will be to assess whether the reported effects of stress on circadian organization are adaptive or maladaptive. It is tempting to think that phase shifts in specific tissues are part of a functional adaptation that allows organism to deal with stressors in the most optimal way, particularly when stressors repeatedly occur at more or less the same time of day. The master clock in the SCN, being mainly sensitive to light, assures that the circadian system, as a whole, remains entrained to the external world. At the same time, peripheral clocks in specific tissues and organs might be responsive to additional signals and inputs that allows them to (temporarily) change their phase and tune their activity for optimal coping with the stressors. For example, tissues and organs involved in energy mobilization and metabolism might respond to stress in the light phase with an advance and to stress in the late dark phase with a delay in order to facilitate optimal physiological and behavioral responses to stress at different times of day. Alternatively, it is not excluded that effects of stress on peripheral clocks are maladaptive rather than adaptive, or maybe start as an adaptive response but eventually develop into a maladaptive state, particularly in case of chronic and uncontrollable stress. It is noteworthy that most studies on effects of chronic or repeated

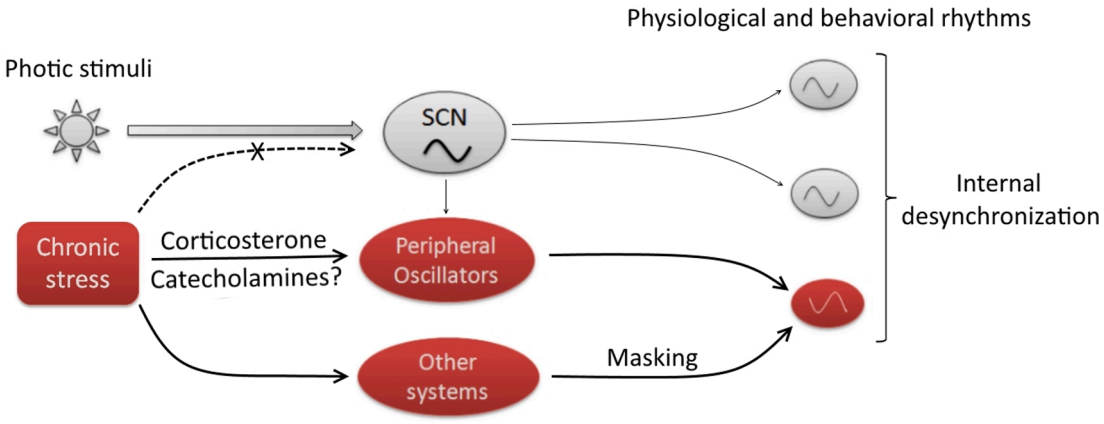

Fig. 6. Chronic stress effects on circadian organization. The master clock in the hypothalamic SCN is synchronized to the external environment by photic input. The phase and period of the master clock do not appear to be affected by stress stimuli. On the other hand, stress and stress hormones (glucocorticoids and catecholamines) at certain times of day can phase shift oscillators in a variety of peripheral tissues, which could result in internal desynchronization between different tissues. In addition, stress and stress hormones may have non-circadian effects on physiology and behavior that can mask the rhythmic output of the circadian system.

stressors applied these stressors at, more or less, regular intervals of around 24 h, often motivated by the question whether these stressors would then be able to entrain peripheral clocks. However, the outcome of exposure to repeated stress might be quite different when stressors occur at unpredictable and random times of day. An initial state of internal reorganization might then gradually develop into a state of internal desynchronization, with the activity of different organ systems no longer optimally tuned with respect to each other. In this case, persistent stress-induced changes in circadian function may very well play a role in the development of diseases, including psychiatric disorders such as depression, metabolic disorders, cardiovascular diseases, and perhaps even cancer (Bass and Lazar, 2016; Daut and Fonken, 2019; Haus and Smolensky, 2006; Stenvers et al., 2019). A strong case for this view is emerging from the collective literature on stress, circadian function, and cardiopathology. Numerous studies have identified stress as a risk factor the development and progression of cardiovascular disease (Kivimäki and Steptoe, 2018). The hypothesis that this relationship may be mediated by circadian disruption is supported by experimental studies in laboratory rodents showing that glucocorticoid stress hormones can shift the cardiac circadian oscillator (Balsalobre et al. 2000; van der Veen et al. 2012). Additionally, experimental studies with animal models have clearly demonstrated that chronic circadian disorganization and internal desynchronization per se can cause sever cardiovascular pathology and even early death (Martino et al., 2008; Martino and Young, 2015). Together, such findings clearly call for further study on the relationship between stress and circadian function.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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