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The circadian system

A regulatory feedback network of periphery and brain

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GENERAL INTRODUCTION

Based upon: The circadian system: A regulatory feedback network of periphery and brain.

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Abstract

Circadian rhythms are generated by the autonomous circadian clock, the suprachiasmatic nucleus (SCN), and clock genes that are present in all tissues. The SCN times these peripheral clocks, as well as behavioral and physiological processes. Recent studies show that frequent violations of conditions set by our biological clock, such as shift work, jet lag, sleep deprivation, or simply eating at the wrong time of the day, may have deleterious effects on health. This infringement, also known as circadian desynchronization, is associated with chronic diseases like diabetes, hypertension, cancer, and psychiatric disorders. In this review, we will evaluate evidence that these diseases stem from the need of the SCN for peripheral feedback to fine-tune its output and adjust physiological processes to the requirements of the moment. This feedback can vary from neuronal or hormonal signals from the liver to changes in blood pressure. Desynchronization renders the circadian network dysfunctional, resulting in a breakdown of many functions driven by the SCN, disrupting core clock rhythms in the periphery and disorganizing cellular processes that are normally driven by the synchrony between behavior and peripheral signals with neuronal and humoral output of the hypothalamus. Consequently, we propose that the loss of synchrony between the different elements of this circadian network as may occur during shiftwork and jetlag is the reason for the occurrence of health problems.

The planet earth revolves around the sun while rotating on its axis every 24 hours. This ubiquitous environmental factor of alternating light and darkness has resulted in almost all organisms being subject to cyclic environmental changes, enforcing a day-night rhythm on their physiology. Adapting to this cyclic world, organisms have evolved circadian (from the Latin *circa*, meaning “approximately”, and *diēm*, meaning “day”) systems synchronizing behavioral and physiological rhythms for optimal anticipation of changes in activity and food availability (Buijs and others, 2006). In mammals the circadian system consists of a central pacemaker, the suprachiasmatic nucleus (SCN), and of peripheral oscillators, found in almost all cell types in brain and body, that resonate with circadian cues originating from the SCN (Lowrey and Takahashi, 2000). Driven by the SCN these oscillators provide rhythmic behavioral, neuroendocrine and autonomic output supporting a circadian organization of physiology. Through SCN endogenous activity, behavioral and physiological rhythms are maintained even in constant dark conditions (DD) (Hastings and others, 2013) allowing organisms to anticipate day-night changes in the environment, best preparing the physiology for upcoming challenges. Since behavioral activity needs to coincide with e.g., increased body temperature, higher circulating glucose levels and elevated blood pressure, the main function of the SCN is to organize these physiological set-points, optimally adapting them to resting or active periods (Kalsbeek and Buijs, 2002).

The molecular clockwork

In the SCN, an oscillatory transcription and translation of genes inside individual SCN neurons takes place. These clock genes are part of an intrinsic oscillator, consisting of interlinked autoregulatory transcriptional–translational feedback loops. This molecular mechanism drives rhythmic, ~24hr expression patterns of core clock proteins, necessary for the generation and regulation of circadian rhythms within individual cells (Reppert and Weaver, 2002). In mammals, the protein complex CLOCK (circadian locomotor output cycles kaput)–BMAL1 (brain and muscle ARNT like protein1)—members of the basic helix-loop-helix (bHLH)-PAS (Period-Arnt-Single-minded) transcription factor family—bound to E-box promoters, form the positive limb of the feedback loop. The negative limb consists of PER-CRY, heterodimers that translocate back to the nucleus suppressing their own transcription by inhibiting CLOCK–BMAL1 activity. Secondary loops are formed with the help of orphan nuclear receptors from the REV-ERB and ROR family, which fine tune the core clock machinery modulating the transcriptional feedback loop, thus contributing to the robustness of the molecular clock (for detailed description see (Partch and others, 2014)). Interestingly, since more than two decades it has been demonstrated that a molecular clock machinery of similar composition is also present in nearly all cells of the body. Importantly, these peripheral clock genes are mainly driven by SCN output, whereby in principle all SCN driven outputs, hormonal (i.e. melatonin and corticosterone) (Balsalobre and others, 2000), behavioral (i.e. activity and food intake) (Damiola and

others, 2000; van Oosterhout and others, 2012), as well as autonomic and physiological (i.e. temperature and glucose) contribute to peripheral clock gene rhythmicity (Brown and others, 2002b; Hirao and others, 2009). Since their discovery, clock genes have been shown to be involved in many different (cellular) functions in peripheral organs, from metabolic function to cell division (Matsuo and others, 2003). Animal models showing tissue specific clock gene deletion have permitted the investigation of the role of certain clock genes in metabolism and investigating their effect on physiology. For example, as a result of liver clock gene disruption, glucose release is altered causing fasting hypoglycemia (Lamia and others, 2008), and decreased hepatic lipogenic gene expression following refeeding after fasting (Zhang and others, 2014). Pancreas clock gene modification results in impaired glucose-stimulated insulin secretion (Sadacca and others, 2011). As in striated muscle fibers, *Bmal1* knockout can cause a fast to slow fiber-type shift and a more oxidative skeletal muscle (Hodge and others, 2015), and in adipose tissue, clock gene knockout can lead to obesity (Paschos and others, 2012). These examples illustrate an essential role for tissue or organ-specific peripheral clock genes and their involvement in adequate physiological regulation.

The clock

The SCN is located above the optic chiasm (suprachiasmatic) through which it receives photic (light) information. This photic information serves to synchronize the activity of the SCN to the daily light-dark cycle. The bilaterally paired SCN is composed of a dense network of approximately 20,000 interconnected neurons (Webb and others, 2009). The SCN, as an autonomously rhythmic nucleus, distinguishes itself from other nuclei in the brain through its structure and function. During the day most SCN neurons are more depolarized, with a resting potential of -45mV approximately. This depolarized state results from the presence of a set of currents (persistent Na⁺, HCN, T- and L-type Ca²⁺) that provides the excitatory drive necessary for any neuron to be spontaneously active (Jackson and others, 2004; Wang and Huang, 2004; Irwin and Allen, 2007). The excitatory drive, mostly present during the day, is then translated into action potentials that induces the transcription of the clock genes *Per1*, *Per2* and *Cry* that in turn modulate the expression of ionic channels (Yamaguchi and others, 2003; Colwell, 2011). Despite that each SCN neuron expresses clock genes and electrical machineries, not all oscillate with the same phase. Each SCN neuron remains active during the day for 4-6 hours (Vanderleest and others, 2007; Meijer and others, 2010). The coordination of these different cycles is arranged through communication within the nucleus enabling a clear and organized output (Welsh et al., 1995; Saeb-Parsy & Dyball, 2003a; Bhumbra et al., 2005). This coordination among the different cells within the SCN is, amongst others, achieved through the presence of gap junctions shared by the different neurons that propagate the electrical activity and by the synaptic association between the neurons by means of VIP, GABA, glutamate and vasopressin transmission within the individual nucleus and glutamate as a transmitter

required for communication between the left and right SCN (Hafner and others, 2012; Brancaccio and others, 2014). In short, it is thought that increased excitability of SCN neurons facilitates spontaneous neuronal activity occurring even in the absence of synaptic drive, thus giving the SCN its endogenous rhythm. At early night the reverse occurs with neurons showing hyperpolarization ($\sim -67\text{mV}$), inhibiting neuronal firing and silencing the SCN (Colwell, 2011). Intercellular coupling and a close association with glia cells (Brancaccio et al. 2017) seems to be critical for a robust endogenously rhythmic SCN which distinguishes it from peripheral oscillators (Mohawk and others, 2012). SCN neuronal rhythmicity is translated into rhythmic release of SCN neurotransmitters, imposing a circadian rhythm onto target neurons. The day-time peak in neuronal activity occurs equally in nocturnal as in diurnal animals, indicating that SCN activity alone does not determine behavioral activity.

Neurotransmitters

The SCN expresses numerous neurotransmitters involved in synchronizing and maintaining an endogenous circadian rhythm of the SCN, whilst also transmitting circadian timed signals to target neurons in the hypothalamus. Based on the anatomical location of these different neural populations, the SCN is generally divided into a ventrolateral and dorsomedial region. In the ventrolateral SCN, associated with integrating external input, gastric-releasing peptide (GRP) and vasoactive intestinal peptide (VIP) expressing neurons receive direct retinal input via the melanopsin containing retinohypothalamic tract (RHT). These neurons convey light-dark information to the rest of the SCN with VIP being critical in maintaining SCN synchrony (Shinohara and others, 1993; Harmar and others, 2002; An and others, 2013). The dorsomedial SCN, i.e., where arginine vasopressin (AVP) and prokineticin 2 (PK2) is expressed, is associated with generating robust circadian rhythms (Albus and others, 2005; Yamaguchi and others, 2013). The neurons expressing AVP display robust self-sustained rhythms in clock gene expression that are necessary for adequate coupling of SCN neurons (Mieda and others, 2015). Accordingly, neuromedin S (NMS) has been shown to be important for keeping the SCN pacemaker-neurons synchronized (Lee and others, 2015). Also GABA (co-expressed in GRP, VIP and AVP neurons) is essential in synchronizing SCN neurons, adapting their activity through both excitatory and inhibitory modulation (Colwell, 2011). Interestingly, exposure to long day photoperiods changes GABAergic activity from inhibitory to excitatory, destabilizing SCN rhythmicity and possibly affecting its sensitivity to photoperiodic entrainment (Farajnia and others, 2012). The ventral and dorsal SCN show elaborate neuronal interconnectivity with the majority running from the ventral to dorsal area (Romijn and others, 1997), underlining the essential role of internal SCN communication.

Finally, coordination of rhythmicity among different cells within the SCN is achieved through intercellular coupling by the presence of gap junctions, glial network encoding, phase-dependent coupling through non-redundant VIP and GABA signaling, paracrine signaling and through glutamatergic communication between the left and right SCN (for review see, Colwell, 2011).

The SCN drives rhythms in behavior, hormone secretion and organ function.

The endogenous rhythm in electrical activity of many SCN neurons (Colwell, 2011; An and others, 2013) is the basis for the rhythmic release of SCN neurotransmitters at their terminals (Buijs and Kalsbeek, 2001). However, in the rat many neurons show a—non-rhythmic—low constant neuronal activity. For example, via constant release of glutamate in the PVN, the SCN promotes melatonin release from the pineal which can only be prevented by the diurnal rhythm of SCN-induced release of GABA in the PVN (Perreault-Lenz and others, 2004). Nonetheless, the majority of SCN neurons are more active during the light period than during the dark (Meijer and others, 1997). Light is a very powerful stimulus for neuronal activation of the retino-recipient portion of the SCN, both during the day as well as at night (Meijer and others, 1998). This activation results in inhibition of locomotor behavior, at least partially, by the release of Prokineticin 2 from SCN terminals (Cheng and others, 2002). The daily light/dark cycle synchronizes SCN neurons to a precise 24 hr rhythm, translated into appropriate behavior according to the time of day and the corresponding hormonal and autonomic signaling (Buijs and Kalsbeek, 2001). This SCN output serves to drive the functionality of the organs both through the induced rhythm of clock and other genes in the organs (Oster and others, 2006; Paschos and FitzGerald, 2010) and by the circadian rhythm of autonomic output (Ishida and others, 2005).

Peripheral oscillators synchronized by the SCN

In the brain, apart from the SCN, autonomous cellular rhythms are found in the olfactory bulb and retina, while other structures, like the Arcuate nucleus (ARC), are able to express an independent rhythm for some time in vitro (Tosini and Menaker, 1996; Granados-Fuentes and others, 2006; Guilding and others, 2009). The general view is that clock genes in non-brain tissues are not autonomously rhythmic; they derive their rhythm from the SCN or from SCN driven processes. The loss of rhythm in peripheral organs following SCN lesions is probably due to the limited intercellular communication in peripheral organs and the loss of synchronizing corticosterone (Balsalobre and others, 2000; Su et al. 2016) or melatonin rhythm. This demonstrates the role of the SCN as synchronizer of peripheral rhythmicity, which is realized through various, still not fully understood pathways. First, autonomic output is capable of driving clock gene expression (Terazono and others, 2003), although autonomic denervation of an organ does not abolish clock gene rhythmicity (Cailotto and others, 2005). Second, glucocorticoids influence clock gene expression but adrenalectomy does not abolish rhythmicity (Balsalobre and others, 2000). Third, food intake during the resting phase, though also affecting temperature and glucocorticoid rhythms, completely reverses clock gene expression in the liver, kidney, heart and pancreas (Damiola and others, 2000), showing that food intake is an essential synchronizing signal for peripheral organs. However, under fasting conditions the rhythm in the liver persists for at least one cycle as it does in food synchronized SCN lesioned animals (Sabath and others, 2014). Fourth, SCN lesioned animals sharing their blood

circulation with intact animals develop a rhythm in clock gene expression in the liver and kidney, indicating that circulating factors are important for their rhythmicity (Guo and others, 2005). Lastly, temperature, too, is capable of altering clock gene expression in the liver (Brown and others, 2002a).

Essentially, peripheral clock genes are guided by direct and indirect signals from the SCN and can be altered significantly in their expression and phase by behavior that is not in line with SCN signaling. This is adeptly illustrated by a recent study demonstrating that animals receiving food 6 times a day, lose their rhythm in white adipose tissue in 7 out of 9 tested oscillatory metabolic/adipokine genes, but not the rhythm of clock genes. Abolishing the daily corticosterone peak also rendered the clock genes arrhythmic (Su and others, 2015). This shows that metabolic genes do not only depend on clock genes for their rhythm but may depend on other processes as well. Nonetheless, supporting a fundamental role for clock genes in peripheral organ function, are studies demonstrating that tissue specific deletion of a single core clock gene, fundamentally changes the functioning of the liver, white adipose tissue or blood vessels (Lamia and others, 2008; Paschos and FitzGerald, 2010; Paschos and others, 2012). Seemingly the mere presence of clock genes is essential for the expression or suppression of regulatory genes present in tissues and organs, organizing a cascade of rhythms (reviewed in (Kolbe and others, 2015). Several studies have reported important functional relationships between clock genes and cellular mechanisms, though the majority of these studies were conducted in vitro, thus ignoring the other components of the in vivo circadian system. Hence caution seems in place in extrapolating such conclusions and it is needed to corroborate these findings by in vivo studies. For example, in spite of in vitro data suggesting the direct production of nicotinamide phosphoribosyltransferase (NAMPT) via CLOCK/BMAL1 (Ramsey and others, 2009) it has been observed that in animals eating during the light period, nicotinamide adenine dinucleotide (NAD⁺) and NAMPT together with some metabolic genes do not follow the inversion of rhythm in core clock genes (Salgado-Delgado and others, 2013). These observations indicate that in vivo, alternative essential molecular relationships prevail; likely driven by other components of the circadian system such as the melatonin or corticosterone rhythm. Importantly, the inversion of clock gene rhythmicity in the liver induced by an inverted feeding pattern is accompanied by severe liver steatosis and insulin insensitivity (Salgado-Delgado and others, 2013); raising the question, why these feeding induced changes in peripheral clock gene rhythms change the physiology of the organism as a whole and why these changes induce liver steatosis. This also brings us to the general scope of this thesis where we investigated possible feedback networks to the SCN, hypothesizing thereby its possible role as integrator of peripheral feedback essential for regulating circadian oscillations in physiology.

The hypothalamus as integrative neuronal network regulates physiology

SCN projections reach many different target neurons—interneurons, endocrine neurons, pre-autonomic neurons and neurons that gate physiologically relevant sensory information (Buijs and others, 2013)—through which a wide range of effector organs are reached who have a somatotopic representation in the SCN (Kreier and others, 2005). This not only provides an anatomical framework for the SCN to spread circadian signals to hypothalamic targets, it also allows the SCN to modulate the access of information entering the hypothalamus. Till recently it was assumed that the SCN would execute its functions by means of timed output that was only synchronized by the light/dark cycle. However, light is not the sole input or synchronizer of the SCN, also melatonin (Sloten and others, 2002), food (Mendoza and others, 2008), blood pressure (Buijs and others, 2014) and locomotor activity (Schaap and Meijer, 2001) have a direct effect on SCN neuronal activity or its phase. Somatic information is received through various direct projections from i.e., the nucleus tractus solitarius (NTS), the intergeniculate leaflet (IGL), ARC, limbic system and raphe nucleus (Malek and others, 2007; Saderi and others, 2013; Buijs and others, 2014). In the present thesis we investigated the possibility whether the SCN could be part of a large network of oscillators all functioning within a series of feedback loops maintaining the organism in synchrony with its environment. In support of this hypothesis are recent studies illustrating functional input to the SCN from circumventricular organs, brainstem viscerosensory nuclei and hypothalamic integration nuclei (Yi and others, 2008; Owen and others, 2013; Bookout and others, 2013).

Scope of the thesis

The general hypothesis of this thesis states that the SCN is not solely an autonomous master clock imposing its rhythm onto the periphery, but depends on peripheral feedback in order to effectively regulate physiological functions. Hereby we investigated whether the SCN needs to receive feedback in order to adequately regulate circadian oscillations in physiology. We hypothesized that generating and synchronizing physiological daily rhythms depends on the integration of photic and non-photoc input in the SCN, whereby the SCN receives feedback information of the physiological state of the body through existing strong neuronal interconnectivity with other hypothalamic nuclei. As such we investigated cardiovascular, metabolic and reproductive feedback- and regulatory circuits with the SCN at its core.

Blood pressure has long been shown to follow a ~24 hour rhythm with a critical role for the SCN independent of behavioral activity (Scheer and others, 2005) for timing of cardiovascular control. In **chapter two** we hypothesized that the SCN, like virtually any structure in the brain, would need feedback to execute its function properly. Therefore, we investigated whether the SCN is incorporated in a brain circuit controlling BP. We looked at the projections of the NTS because this nucleus in the brain stem is the central relay in forwarding visceral and thus also cardiovascular, sensory information to the brain. Retrograde and anterograde tracing studies were performed to determine whether the SCN indeed receives projections from the NTS to the SCN. We also looked at the functionality of this connection by examining the differential activation of the SCN following blood pressure elevations and monitoring blood pressure responses after placing SCN lesions in Wistar rats. In **chapter three**, we further focused on the SCN as integration center of cardiovascular information and demonstrated how cardiovascular input can influence SCN output by examining changes in activity of the SCN-parasympathetic neuronal pathway following olanzapine and melatonin administration.

In view of the influence of cardiometabolic changes on the SCN and considering early reports that metabolic changes influence neuropeptide Y (NPY) concentrations in the SCN (Park et al. 2004) and that phase advances induced by time and caloric feeding restriction are appreciably decreased in IGL-lesioned rats (Challet, Malan, and Pévet 1996), we hypothesized in **chapter four** that the IGL—known as providing the SCN with photic and non-photoc information via its NPY innervation amongst others—provides the SCN with metabolic related information. Using male Wistar rats in different metabolic states (fed, fasted and ad libitum) and by lesion studies performed either in the ARC or in the IGL we investigated a novel circuit involving the IGL in mediating metabolic information to the SCN. Considering that the ARC is the main sensory structure for metabolic information and in view of recent observations that lesions targeting specific neuronal populations in the ARC resulted in deteriorated temperature, feeding and sleep rhythms (Li and

others, 2012; Wiater and others, 2013) we hypothesized that the ARC could provide an essential feedback pathway to the SCN, adjusting its output and facilitating changes in its neural activity in response to physiological and behavioral activity. In **chapter five** we thus studied the nature of ARC-SCN interconnectivity by placing knife cuts between the SCN and ARC. We observed loss in rhythms in locomotor activity, body temperature and corticosterone levels as well as changes in clock gene rhythmicity showing the importance of ARC-SCN network properties in organizing physiological functions. In **chapter six** we investigated the role of different hypothalamic areas including the ARC, the anteroventral periventricular nucleus (AVPV) and SCN in the complex regulation of the reproductive cycle. We hypothesized that similar to neurons in the dorsomedial hypothalamus (DMH), Kisspeptin neurons—involved in regulating reproductive function—form a feedback circuit with the SCN. Through immunohistochemistry and tracing studies we examined Kisspeptin projections from the AVPV and ARC to the SCN. Finally, in the general discussion—**chapter seven**—the results are placed in a broader perspective focusing on the importance of a balance between the different systems whose activity is influenced by the circadian system and we argue that consequently circadian desynchronization is associated with chronic diseases like diabetes, hypertension, cancer, and psychiatric disorders. We examine evidence that these diseases stem from the SCN requiring peripheral feedback to fine-tune its output and adjust physiological processes to the requirements of the moment. Subsequently, we discuss how the loss of synchrony between the different elements of this circadian network as may occur during shift work and jet lag can contribute to the development of health problems and disease. We end this thesis with a perspective on and recommendations for future research to further unravel the role of feedback to the SCN within the circadian system and how a more broad application of timed therapeutic intervention could improve treatment outcome for patients.

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