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Review

The suprachiasmatic nucleus; a responsive clock regulating homeostasis by daily changing the setpoints of physiological parameters

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ABSTRACT

The suprachiasmatic nucleus (SCN) is responsible for determining circadian variations in physiological setpoints. The SCN achieves such control through projections to different target structures within and outside the hypothalamus. Thus the SCN prepares the physiology of the body every 24 h via hormones and autonomic nervous system (ANS), to coming changes in behavior. Resulting rhythms in hormones and ANS activity transmit a precise message to selective organs, adapting their sensitivity to coming hormones, metabolites or other essentials.

Thus the SCN as autonomous clock gives rhythm to physiological processes. However when the body is challenged by infections, low or high temperature, food shortage or excess: physiological setpoints need to be changed. For example, under fasting conditions, setpoints for body temperature and glucose levels are lowered at the beginning of the sleep (inactive) phase. However, starting the active phase, a normal increase in glucose and temperature levels take place to support activities associated with the acquisition of food. Thus, the SCN adjusts physiological setpoints in agreement with time of the day and according to challenges faced by the body. The SCN is enabled to do this by receiving extensive input from brain areas involved in sensing the condition of the body. Therefore, when the body receives stimuli contradicting normal physiology, such as eating or activity during the inactive period, this information reaches the SCN, adapting its output to correct this disbalance. As consequence frequent violations of the SCN message, such as by shift work or night eating, will result in development of disease.

1. Introduction

1.1. The central clock synchronizes physiology

It is now established that 24 h rhythms in neuronal activity of SCN neurons depend on clock genes whose products (transcriptional activators and repressors) modulate protein stability and nuclear translocation through interlocking feedback loops (Reppert and Weaver, 2002; Etchegaray et al., 2003; Okamura, 2007; Takahashi et al., 2008). It is through this mechanism that neurons of the SCN can collectively, even in vitro, maintain a circadian rhythm in their discharges (Green and Gillette, 1982; Groos et al., 1983): the SCN consists of numerous groups of neurons, with each group having its own rhythm. The interaction of these groups with each other is essential for maintaining an autonomous rhythm in neuronal activity of the whole population of SCN neurons (Aton et al., 2005; Yamaguchi et al., 2013). When SCN cells are dispersed in vitro, more and more neurons lose their rhythmicity, which raises the question as to whether individual SCN neurons are intrinsically capable of maintaining their 24 h rhythmicity (Webb et al., 2009). This question is relevant since all cells of the body and CNS neurons express clock genes, yet they do not necessarily show the same rhythmic capacity as SCN neurons, even if they may become synchronized by a strong stimulus (Kaeffer and Pardini, 2005).

When placed in vitro, mammalian organs, in contrast to those of insects and fish, lose their rhythm after a few cycles (Giebultowicz, 2001). However, as peripheral tissues in insects and zebra fish keep their sensitivity to light, they can adjust their phase depending on light input: i.e., as light can penetrate their whole body the development of a central clock is not essential for the synchronization of their different clock clusters (King et al., 2017). In comparison, in mammals light can only adjust the rhythm of SCN neurons through the influence of retinal input on a specific set of ventrally positioned SCN neurons (Jones et al., 2018). In constant dark conditions the majority of the SCN neurons have their highest neuronal activity during the subjective light phase, which however does not mean that all SCN neurons are silent during the subjective dark phase (Hermanstyne et al., 2016); e.g., SCN neurons

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responsible for melatonin secretion, are active during the dark phase (Perreau-Lenz et al., 2004).

The circadian rhythm in neuronal activity of SCN neurons results in a time dependent release of various transmitters in the target areas of SCN neuronal projections, thus conducting the circadian signal to numerous CNS regions. The dissemination of this signal results in an organization of behavior such that animals are active (e.g., food foraging) mainly during particular times of the light dark cycle. In parallel, the SCN also regulates hormonal and autonomic output in order to support such changes in behavior. In this manner, in all tissues of the mammal, clock genes and their proteins become rhythmic, which is essential for many cellular processes. Without the SCN, an animal loses its capacity to synchronize its various functions through loss of its capacity to synchronize the clock genes of various organs. Therefore, the main task of the SCN in the mammalian body is to synchronize bodily functions to the light dark cycle to ensure that an animal can operate optimally within its environment.

Recent studies have shown that human behavior not coinciding with the signals of the biological clock and thus promoting desynchronization may lead to a variety of disorders such as obesity, hypertension, diabetes and cancer. The possible mechanisms for the development of these diseases will be examined in this review.

2. SCN circadian control

2.1. The ANS is an important efferent arm of circadian control of physiology

The pre-autonomic neurons of the paraventricular nucleus (PVN) are the main targets where the SCN influences monosynaptically the hypothalamic output to the main vagal motor nuclei and the sympathetic preganglionic motor neurons of the spinal cord. This allows the SCN to influence the parasympathetic and sympathetic output to all organs. For example, via its projections to the PVN, the SCN increases the sympathetic output to the liver just before the active period, resulting in an increase in glucose production (La Fleur et al., 1999; La Fleur et al., 2000). At the same time, the sympathetic output to the adrenal is increased resulting in a simultaneous increase in corticosterone secretion (Buijs et al., 1999), while the SCN is promoting glucose uptake in the muscles (La Fleur et al., 2001), probably also via sympathetic activation (Shimazu and Minokoshi, 2017). Additionally, in the dark phase, sympathetic induced secretion of melatonin from the pineal gland, is induced via a direct SCN input to PVN pre-sympathetic neurons. Light, through its activation of other SCN neurons, immediately inhibits (via the release of GABA) the same PVN neurons resulting in an immediate halt of melatonin secretion and lowering of heart rate (Scheer et al., 2003; Perreau-Lenz et al., 2003). Such observations illustrate the importance of the sympathetic system in circadian control: much less is known about the control or influence of the parasympathetic system. We assume that its main importance is to keep the sympathetic influence on the organs in balance.

The question arises as to whether the same neurons in SCN or PVN are able to influence both sympathetic and parasympathetic output. Retrograde pseudorabies virus (PRV) tracing studies provide evidence consistent with the idea that preganglionic parasympathetic and sympathetic motor neurons receive input from different SCN neurons (Buijs et al., 2003). Moreover, different sympathetic projecting neurons target distinct organs, thus providing the anatomical basis for differential control; e.g., in humans, a *high* sympathetic drive to the pineal at night coincides with a *low* sympathetic drive to the heart (Kreier et al., 2005). In addition, studies examining the autonomic control of fat tissue demonstrate that subcutaneous fat tissue sympathetic input is influenced by different SCN neurons than sympathetic input to intra-abdominal fat tissue. Similarly, different populations of SCN neurons appear to regulate parasympathetic input to those fat compartments (Kreier et al., 2002). The fact that different neurons in the SCN and other parts of the CNS can control the accumulation and burning of fat in different compartments may explain how it is possible to have a body fat distribution with more abdominal fat than subcutaneous fat as seen in metabolic syndrome, hypertension and diabetes. Consequently, such disease states might be related to aberrant autonomic regulation (Kreier et al., 2003).

2.2. SCN circadian control of hormone secretion

The circadian rhythm in hormone levels is either induced by the SCN directly via multi-synaptic neuronal pathways or via the influence of the SCN on behavior such as food and water intake or locomotor activity; e.g., leptin increases during food intake in rats (Kalsbeek et al., 2001), ghrelin increases after a fasting period (Shiiya et al., 2002), and adrenalin increases associated with locomotor activity (De Boer and Van Der Gugten, 1987); all oscillate in a daily fashion and are mainly controlled by SCN driven behavior. The hormones released from neurons influenced by the SCN monosynaptically or multisynaptically are secreted into the external zone of the median eminence to induce the release of adenohypophysial hormones (Neumann et al. 2019). Here we will give as an example two of the best studied hormones; gonadotrophin releasing hormone (GnRH) and corticotrophin releasing hormone (CRH). Neurons producing these releasing hormones receive direct and indirect input from the SCN. VIP terminals originating from the SCN contact directly GnRH neurons (Van Der Beek et al., 1993) while vasopressin fibers arising from the SCN target Kisspeptin neurons which provide a stimulatory input to GnRH neurons (Van Der Beek et al., 1993; Williams III et al., 2011). The inhibitory input to GnRH neurons is thought to come from RFRP3 neurons located in the dorsomedial nucleus of the hypothalamus (DMH) (Klosen et al., 2013). Also, these inhibitory neurons receive an input from the SCN, putting the circadian system in an excellent position to precisely time GnRH release and thus the LH surge. Finally both RFRP3 neurons and the Kisspeptin neurons provide a feedback to the SCN completing the circle for the circadian system (Acosta-Galvan et al., 2011).

The clear rhythmicity of corticosterone secretion in mammals also finds its basis in a direct and indirect control by the SCN. Tracing studies revealed that there are very limited monosynaptic SCN projections to corticotrophin releasing hormone (CRH) neurons. Yet the daily rhythm in corticosterone is explained by the SCN projections to the DMH which has extensive projections to the PVN and serves to transmit the SCN signal to CRH neurons and pre-autonomic neurons in the PVN (Kalsbeek et al., 1996). Notably the day night variations in ACTH in the circulation hardly show any circadian variation (in the beginning of the light phase 70 ng/L versus at the end of the light phase 80 ng/L), indicating that other mechanisms need to be in place to explain the 50 fold difference in corticosterone secretion at the same times. Several studies have demonstrated that the sympathetic input to the adrenal is responsible for the enhanced corticosterone secretion (Engeland and Gann, 1989). Consequently, the SCN influences the adrenal cortex both via the ANS and via the liberation of ACTH, but the main influence is via the ANS (Buijs et al., 1999; Ishida et al., 2005). Interesting in this respect is that also for the negative feedback of corticosterone a double system is in place. The CRH neurons in the PVN have the glucocorticoid receptor (GR), thus allowing glucocorticoids to inhibit CRH and thus ACTH secretion. However, the autonomic neurons in the PVN, responsible for the autonomic control of corticosterone secretion, do not express the GR (Leon-Mercado et al., 2017) and thus cannot sense circulating corticosterone. Recently however, it was demonstrated that the fast negative feedback of corticosterone secretion is arranged via sensing of corticosterone in the arcuate nucleus, where neurons that project to the PVN autonomic neurons do have the GR. Since glucocorticoids cannot pass readily the blood brain barrier, but can pass freely the median eminence area, the arcuate nucleus is able to sense rapidly circulating corticosterone levels, thus adjusting the endocrine adrenal output via its projections to the preautonomic neurons in the PVN

(Leon-Mercado et al., 2017). This fast control, may be an alternative mechanism used by circulating hormones and metabolites to communicate with control centers in the brain via the arcuate nucleus for fast feedback. These examples illustrate the possible mechanisms via which the SCN may regulate the functioning of the endocrine and other organs of the body, see also for other aspects this volume, Neumann et al. 2019.

In short, considering the rhythmic output of organs it is clear that the autonomic and hormonal input driven by the SCN have an essential function. Then the question arises, what is the role of the clock genes for the rhythmic functions of these organs?

3. In search of the functionality of peripheral clocks

3.1. Importance of clock genes in peripheral tissues

The question about the importance of clock gene rhythms seemed to be answered by a series of studies demonstrating that organ specific knockouts of clock genes (mostly Bmal1) resulted in the dysfunction of the organ, suggesting an essential role of the "clock" in these organs (e.g., Lamia et al., 2008). However, this does not necessarily mean that the *clock* as an autonomous clock is important in these organs. It might mean that because of the deleted clock gene some essential proteins are missing that are crucial for at least part of the function of the organ. This is illustrated by an experiment carried out to determine the reason for the pathology occurring in Bmal1 −/− animals (McDearmon et al., 2006). They produced transgenic mice that constitutively express Bmal1 in brain or muscle and examined the effects of the rescued gene expression in Bmal1 −/− mice. The results showed that circadian rhythms of wheel-running activity were restored in brain-rescued Bmal1 −/− mice; however, activity levels and body weight were lower than those of wild-type mice. In contrast, muscle-rescued Bmal1 −/− mice displayed normal activity levels and body weight, yet the animals remained arrhythmic. Importantly only 75% of brain-rescued mice survived to the end of the experiment (6–9 months), whereas all muscle-rescued mice survived. These results show that deleting or over expressing Bmal1 in a cellular system outside the SCN does not induce only a malfunctioning of the clock, it rather indicates that certain cellular/metabolic processes in that system are affected. For example, the occurring deficits of conditional knockouts in certain organs might be induced because Bmal1 protein is missing in development. When Bmal1 is deleted in adult animals, fewer organ functions are affected (Yang et al., 2016), indicating important (possibly non-clock) functions for Bmal1during early development. Another possible reason why an organ may develop serious pathology while missing one clock gene may be that it can no longer be properly synchronized by the SCN.

3.2. Synchronization of rhythmicity of an organ and between different organs is clearly imposed by the SCN

Without the central clock, all circadian rhythmicity in organ functions is lost. Several studies have investigated how the SCN may transfer its rhythm to peripheral organs by examining the rhythm in clock genes. For example, the SCN could drive the rhythm in clock genes in the adrenal gland via the rhythm in ACTH secretion and/or via the ANS. The continuation of adrenal clock gene oscillation in hypophysectomized animals indicates that the rhythm of the adrenal clock genes is independent of SCN signaling via the pituitary gland (Fahrenkrug et al., 2008). On the other hand, light influences not only the release of corticosterone but also the expression of clock genes in the adrenal gland (Ishida et al., 2005). Finally, in hamsters that show split rhythms of locomotor activity and corticosterone secretion in constant light, a split rhythm in the left and right SCN coincided with a split rhythm in the left and right adrenal clock genes (Mahoney et al., 2010). This shows that the SCN via the ANS influences, in addition to corticosterone secretion, the rhythm of the clock genes in the adrenal.

Recently, in a search for a functional role of the clock genes in the adrenal for corticosterone secretion, Dumbell et al. (2016) made a Cre-loxP-mediated conditional knockout of Bmal1 in the steroidogenic cells of the adrenal cortex and observed that animals with such a conditional loss of Bmal1 still showed a rhythm in corticosterone, indicating that the clock mechanism within the adrenal is not essential for the rhythmic release of corticosterone (see also this volume Neumann et al. 2019). Likewise, Cailotto et al. (2005) demonstrated the absence of a rhythm in glucose in the circulation after sympathetic denervation of the liver, while the rhythm in liver clock genes was unaltered. We recently determined which factors are essential for the rhythm of clock genes in the liver and showed that both a rhythmic food intake as well as a rhythm in corticosteroids, is essential for the rhythm in clock genes in the liver; without either of these two, the rhythm is gone (Su et al., 2016). Consequently, these studies support the idea that in spite of the attractiveness of the concept, that clock genes arrange all rhythms in our peripheral organs, they seem to be merely a contributory factor to optimal organ functionality.

Different organs have different rhythms and different needs. These requirements need to be carefully allocated. What is the synchronizing function of the SCN? We can hypothesize that organs need to be tuned carefully, such that for example, in preparation for activity, glucose production of the liver coincides with glucose uptake in the muscles and heat production of brown adipose tissue. The synchronization of clock genes and the associated proteins in our organs is a part of that balance. This important issue of synchrony and coordination of different body systems will be the point of discussion in the next few paragraphs.

4. Coordination between autonomic and behavioral functions: the communication between peripheral tissues and CNS

Behavior is generated by the needs of the tissues of which the needs of the CNS have the first and dominant position: if the CNS senses a disturbance in its environment (e.g., glucose levels, state of hydration, oxygen supply), the drive to correct this disruption of homeostasis must dominate. Thus, in a hypoglycemic state the CNS starts and coordinates processes, both behavioral and internal, to enhance glucose levels in the circulation; e.g., regulate sympathetic drive to liver, fat tissue and adrenal medulla (releasing adrenalin) to produce a rise in blood glucose, and initiate the appropriate feeding behavior to sustain the availability of glucose. Therefore, the CNS needs to be informed in real time about the state of the tissues, in order to be able to contribute appropriately to the regulation of their function. This influence of feedback, concerning the physiological state of the body, on behavior, on control of internal environment and on CNS processes, can be illustrated by the power of angiotensin to stimulate water intake or of ghrelin to stimulate food intake (Epstein et al., 1970; Asakawa et al., 2001).

Such interactions between peripheral tissues and CNS may explain certain CNS diseases: it is known that the majority of depressed patients have at least one co-morbidity (Wells et al., 1991; Grover et al., 2017); e.g., a high co-morbidity with pathologies generating pain, hypertension and obesity. Therefore, understanding how physiological information about the state of peripheral tissues is transmitted to the CNS requires consideration.

4.1. Signaling the state of the peripheral tissues to the SCN

As we have seen above, the SCN needs to be informed about the state of tissues in order to regulate physiology. Despite the equal importance of this communication for the function of the organism, much less is known about how information regarding the state of peripheral tissues influences SCN function, than about how the SCN regulates the functions of peripheral tissues. The SCN is informed about the state of the peripheral tissues via the same three routes that it uses to control peripheral tissue function.

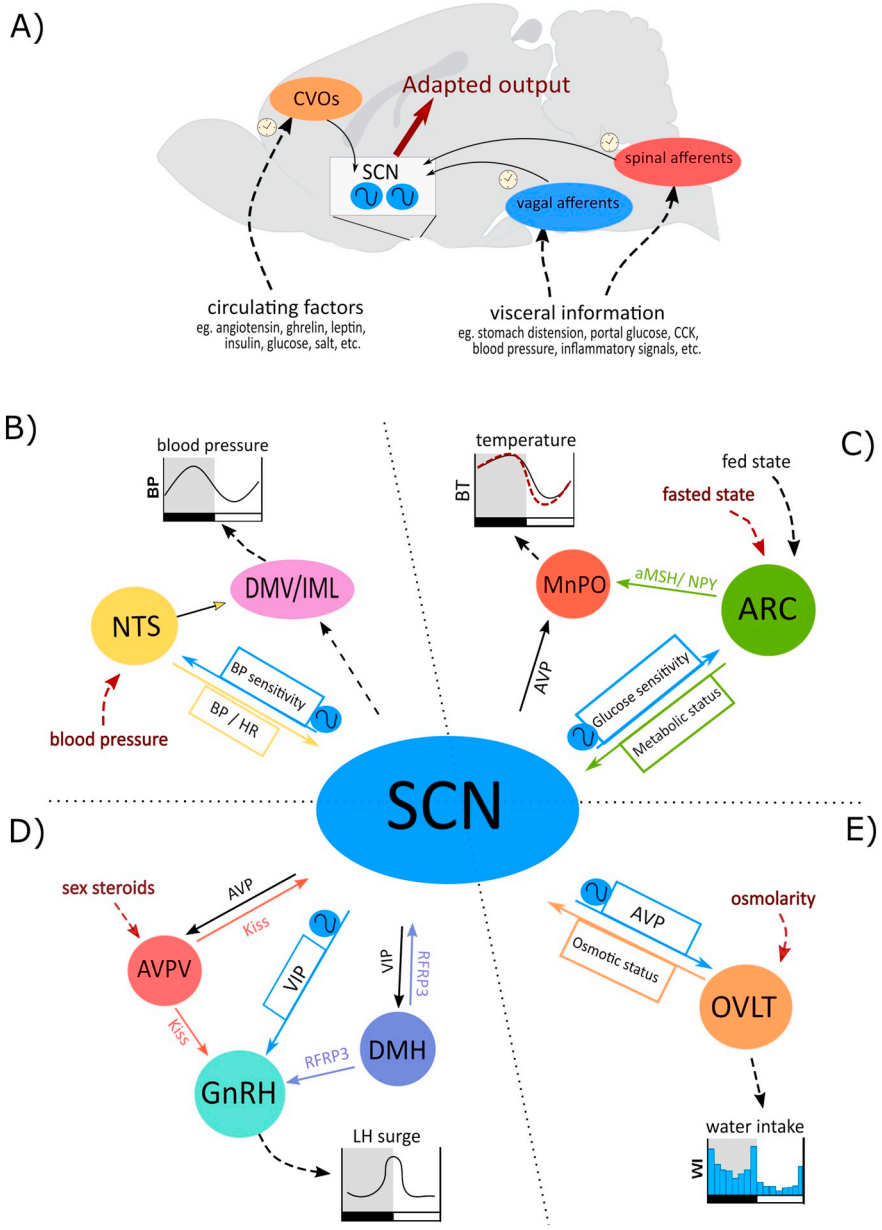

Fig. 1. Circadian organization of physiology, a feedback network including the SCN.
A) Feedback provided to the SCN through different pathways: **circulating factors** is received by the brain via the Circumventricular Organs (CVOs), that integrate information about humoral information; while **visceral information** is integrated by vagal and spinal afferents. All information has a rhythmic profile and is integrated by the SCN, which will **adapt its output** to adjust physiology according to the specific requirements of the organism.
B) The SCN sets the Blood Pressure (BP) rhythm via multi synaptic pathways to the Dorsomotor Nucleus of the Vagus (DMV) and Intermediolateral Medulla (IML). Changes in BP are transmitted to the Nucleus of the Solitary tract (NTS) that projects to the SCN. Also, the SCN projects directly to the NTS possibly to sets its sensitivity for BP changes.
C) The reciprocal connections between SCN and the ARC nucleus are essential for the generation of the rhythm in body temperature (BT). The SCN modulates the daily activity of the ARC nucleus, changing its day-night responses to metabolic cues like glucose levels, in turn the ARC sends information about the metabolic status of the body back to the SCN, in order to adjust its output. Both nuclei project to thermoregulatory centers such as the Median Preoptic Nucleus (MnPO), the SCN via vasopressin (AVP) and the ARC via a-MSH and probably NPY. The integration of the combined signals determines the moment when the BT needs to decrease further than normal (i.e. fasting condition) in order to save valuable energy needed for the active phase.
D) The LH surge is a complex physiological process relying on the integration of temporal and metabolic information. Kiss neurons in the anteroventral periventricular nucleus (AVPV) integrate temporal information conveyed by AVP from the SCN and by sex steroids from the periphery and target GnRH neurons to induce the preovulatory LH surge. The dorsomedial nucleus of the hypothalamus (DMH) also times the surge by relaxing the inhibition of GnRH neurons through RFPR3 neurons. VIP from SCN also is involved in this inhibition by projecting to DMH RFPR3 neurons and directly to GnRH neurons. SCN receives feedback both from RFRP3 as well as Kiss neurons.
E) AVP released from SCN in the OLVT induces water intake just before the onset of the resting phase, the OVLT is mostly involved in sensing the osmotic status of the body and it is known to project to the SCN, the implication of this interaction in terms of feedback has not been studied but we propose it may signal the osmolarity of the blood.

4.1.1. Circulation

Due to their chemical nature, some hormones like melatonin or gonadal steroid hormones are thought to pass the blood brain barrier and thereby signal directly to the CNS. Nevertheless, this is not the only way by which circulating substances signal to the CNS. An ever increasing number of substances and hormones are known to signal to the CNS via the circumventricular organs (CVO). These CVOs have a more permeable blood-brain barrier allowing circulating substances to pass and thus they play a role as sensory structures for circulating substances: the sensory structures are the area postrema in the brain stem, the median eminence - arcuate nucleus, the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) in the hypothalamus. Not surprisingly, the SCN receives information directly from all these CVOs except the area postrema (Lind et al., 1982; Saeb-Parsy et al., 2000; Gizowski et al., 2016). The substances that are sensed can vary from glucose and sodium to hormones like leptin, ghrelin, corticosterone, angiotensin and insulin to signaling molecules like cytokines. The CVOs sense these substances and signal this information to the hypothalamus including the SCN and the brainstem. In this manner the circle is closed and the SCN can use information obtained from the periphery to influence tissue function and behaviors through hormonal and/or autonomic and somatic efferent pathways. Clearly, information transmitted via the circulation reaches the CNS in seconds or longer. Evidence that the SCN can be informed about the state of our organs in milliseconds indicates that cranial and spinal afferents are essential.

4.1.2. Cranial afferents

Cranial afferents (glossopharyngeal and vagal), are known to be important for the transmission of cardiovascular and gastrointestinal information, which is transmitted to the NTS in the brainstem. Recently, it was demonstrated that a gut epithelial sensor cell -the enteroendocrine cell- has close contacts with vagal afferents to transduce gut enteric signals in milliseconds. This neuroepithelial-vagal interface links the intestine to the brainstem allowing the CNS to sense gut stimuli (Kaelberer et al., 2018). In another study such gut-innervating vagal afferents were shown to be able to stimulate CNS reward neurons; activation induced dopamine release from substantia nigra into the nucleus accumbens/striatum, and conditioned both flavor and place

preferences, and promoted sustained self-stimulation behavior (Han et al., 2018). These new data add chemical precision to previous evidence that stretch sensitive vagal afferents are also able to transmit organ volume to the central nervous system (Williams et al., 2016; Prato et al., 2017). These type of communications are not restricted to stomach or gut, as other studies show that the liver, lung and other tissues also may signal essential information about their physiological state to the CNS via vagal afferents (Uno et al., 2006; Chang et al., 2015). Considering what has been discussed previously, concerning how via the ANS the SCN can influence the output of the organs and blood pressure, it is important to note that a reciprocal connection between SCN and NTS was shown to be relevant for the adjustment of cardiovascular tone (Buijs et al., 2014). Consequently, these data provide the anatomical and functional basis for the feedback of important physiological information from peripheral organs to the SCN.

4.1.3. Spinal afferents

Probably the first to demonstrate the capacity of spinal afferents to transmit non-pain or inflammation related information from peripheral tissues was Niijima (1999) who injected leptin into white adipose tissue (WAT) and was able to demonstrate an increase in spinal afferent discharges followed by an increased firing of efferents destined for brown adipose tissue (BAT). Recently these results were corroborated and extended by several other studies (Xiong et al., 2012; Murphy et al., 2013; Spencer et al., 2016). Since this information entering the spinal cord may be transmitted to the SCN (Yu et al., 2017) these observations support the idea of reciprocal communication, both hormonal and neuronal, between SCN and peripheral tissues. In consequence, the SCN output changes in relation to the extensive feedback it receives about the state of peripheral tissues Such changes are correlated to changes in SCN neuronal activity and the peripheral physiology (e.g., Cheng et al., 2002; Yi et al., 2006) (Fig. 1).

5. The suprachiasmatic nucleus is part of a hypothalamic network regulating homeostasis

5.1. Changing homeostatic setpoints

Many different homeostatic setpoints have a daily rhythm that is determined by the SCN. Many of these setpoints are very tightly regulated and do not show much variation, but may vary under certain conditions. For example, glucose and temperature levels change when an animal is fasted to a much lower level than normal but only at the beginning of the sleep period. However, just prior to the start of the active period glucose and temperature rise to normal levels for that time of the day despite the persistence of the fasting condition. The physiological advantage is clear, the decrease prevents unnecessary use of energy when the animal is sleeping while the anticipatory increase prepares the body for the coming active phase by raising body temperature and glucose levels. Similarly, some other rhythmic physiological conditions show different excursions upon external stimuli that vary over the circadian cycle. Corticosterone secretion after a physical stressful stimulus, for example, is not the same at the beginning of the sleep period (high release) as at the beginning of the active period (low release). For corticosterone release after a physiological stress i.e., hypoglycemia, it is the reverse; low in the sleep and high in the active period (Kalsbeek et al., 2006). Other rhythmic hormone secretions like thyroid stimulating hormone (TSH) or gonadotropin releasing hormone (GnRH) also have their normal circadian peak just before the active period and those peaks are blunted by fasting or stress. The effect of fasting might be directly regulated by an action of FGF21 on the SCN (Bookout et al., 2013) or via the arcuate nucleus (ARC: (Matsuzaki et al., 2011) to the SCN (Buijs et al., 2017). Consequently, in spite of the well-organized and established rhythms of various hormones and metabolites, external stimuli may influence the level of those rhythms in specific and predetermined ways. The question arises: How is the CNS coordinating these very specific responses that relate to the timing of our physiology?

As we have seen, the SCN determines physiological setpoints for the active phase and setpoints for the inactive phase, which can be adjusted depending on specific requirements. In a homeostatic system, the modulation of a certain set point requires the consideration of three issues, and with respect to SCN functionality the following need to be considered (Fig. 1):

a. The ability to modulate the levels of physiological variables.
b. The ability to modulate the sensitivity of various sensors.
c. The ability to receive feedback from the regulated system.

With reference to a), we have considered the endocrine and autonomic outputs that the SCN uses to modulate many aspects of physiology. In the next paragraphs we will discuss the evidence that the sensory input to different control systems may be gated by the circadian clock to adapt central responses. Then evidence will be analyzed that the SCN also receives feedback from several systems to adjust its output.

5.2. Circadian variations in stimulus response characteristics

Insulin sensitivity, as measured by glucose uptake, is modulated in a circadian manner with high sensitivity at the beginning of the active phase and low sensitivity during the resting phase. This increased or decreased uptake is not due to increased or decreased levels of insulin, but to a higher sensitivity to insulin modified by the SCN (La Fleur et al., 2001). Regarding the sensitivity to a hypoglycemic stimulus, intravenous 2DG injection elicits a much higher glucose response at the beginning of the active period than at the beginning of the inactive period. The direct involvement of the SCN in the regulation of the sensitivity to such hypoglycemia was not only demonstrated by the different responses in time, but also by using unilateral lesions of the SCN: The arcuate nucleus showed much more neuronal activation to the hypoglycemic stimulus at the lesioned site than at the non lesioned site, while in addition the glucose response was greatly increased (Herrera-Moro et al., 2016).

The SCN also influences the sensitivity of the arcuate nucleus to glucocorticoid feedback. At the beginning of the sleep phase, where circulating corticosterone levels are low, only the high affinity mineralocorticoid receptors (MR) are occupied, while the low affinity glucocorticoid receptors (GR) are free. At the beginning of the active phase with high levels of circulating corticosterone, both GR and MR are occupied. Therefore, it is only in the active phase that a GR antagonist is able to induce an increase in corticosterone. Apparently the vacant GR receptor in the inactive phase, does not affect corticosterone secretion while being unoccupied at the active phase leads to very high corticosterone levels (Leon-Mercado et al., 2017).

The response to some cranial nerve afferent input, is also modulated in a circadian manner. Regarding taste, sweet and salt recognition is lower in the morning and higher in the afternoon. In contrast, bitter taste has no rhythmic recognition threshold (Fujimura et al., 1990; Nakamura et al., 2008). Considering mechanisms of these sensitivity changes, it is possible that circadian modulation can occur at the level of the receptor. Recordings of gastric vagal mechanoreceptors in ad libitum and fasted mice, show a greater response to mechanical stimulation during the resting phase as compared with the active phase, when the stomach is normally being filled. However, this effect is independent of stomach content, and this rhythm persists even after 72 h under constant dark conditions. In addition, also gastric vagal afferent sensitivity for mechanic stimuli presents a circadian rhythm (Kentish et al., 2016). Intestinal, pancreatic and hepatic sensors for glucose, also exhibit a circadian rhythm, while hexose transporter mRNA and protein levels follow a diurnal rhythm in rat jejunum. The increase of expression of these hexose transporters occurs just before the onset of activity and food intake, thus preparing the intestines for optimal transport of

glucose into the blood stream (Houghton et al., 2006).

There is also a time dependent sensitivity for inflammation: the response to LPS is high during the day and low during the night and this difference is dependent on the SCN (Guerrero-Vargas et al., 2014). Data from our group show that this sensing of LPS-induced molecules takes place in the liver and is transmitted via spinal afferent pathways. The sensing of this inflammatory information is gated at the level of the dorsal horn in a circadian manner. The activation of these dorsal horn neurons leads to the initiation of an inhibitory reflex to the organs that produce the LPS-induced cytokines. Additionally this activation of dorsal horn neurons transmits information to the SCN, resulting in a change in its neuronal activity (Soto-Tinoco et al. unpublished observations).

5.3. Feedback to the SCN from peripheral afferents

Since the SCN is considered an autonomous clock, it is thought that apart from light input, the SCN does not need adjustments or feedback. The arguments are that very few stimuli are able to change the phase or the rhythm of the SCN. However, here we discuss recent evidence indicating that the SCN is part of an extensive circadian feedback network organizing and adjusting the daily settings of a multitude of physiological parameters such as temperature, blood pressure, fluid balance and associated hormones and metabolites. In this manner, the SCN is able to use feedback in order to change its output and thus the output of the CNS, but not the phase of its rhythm in relation the dark-light cycle.

It is established that SCN neuronal activity can change depending on the conditions of the organism; even the sleep phase may change its neuronal activity (Deboer et al., 2003). Individual SCN neurons change their firing rate over the 24 h cycle and respond to external stimuli in a time dependent manner and thus change their firing rate depending on the time of the stimulus. Such stimuli would enable the SCN to incorporate and adapt its output depending on the time of day a stimulus occurs.

Several stimuli that change neuronal activity of SCN neurons, are associated with food intake; e.g., i.p. administration of ghrelin (Yi et al., 2006) leptin (Grosbellet et al., 2015), fasting or refeeding (Saderi et al., 2013) and FGF21(a starvation signal) suppress or change the activity of SCN neurons (Bookout et al., 2013). Further, the SCN also changes its neuronal activity after an inflammatory stimulus (Guerrero-Vargas et al., 2014) or after an increase in blood pressure (Buijs et al., 2014). Finally, as discussed before, the SCN also receives input from areas (e.g., ARC, SFO, OVLT) involved in monitoring circulating information and from areas (e.g., NTS and spinal cord) receiving input from cranial and spinal afferents, respectively. Thus all areas that receive nervous or humoral input from the body, are able to adjust SCN output in relation to the feedback, related to the physiological status. The arcuate nucleus deserves particular attention regarding the importance of its reciprocal interaction with the SCN. Such interaction is illustrated by the observation that interrupting the communication between SCN and arcuate nucleus by means of micro-knife cuts, resulted in a complete loss of corticosterone rhythm, temperature rhythm, and locomotor activity rhythm in constant dark conditions (Buijs et al., 2017).

The functionality of the SCN interaction with the arcuate nucleus, is probably best illustrated by the control of the daily rhythm in temperature. This daily rhythm is strongly influenced by time as well as by food availability. The SCN controls the daily change in temperature; low in the beginning of the sleep phase and increasing towards the activity phase. However, this daily rhythm is strongly influenced by feeding opportunity: fasted animals show a more pronounced drop in body temperature in the beginning of their sleep phase (Bt) than at any other time. This pronounced temperature drop does not occur in an SCN lesioned animal (Liu et al., 2002). The explanation for this is that the SCN not only changes the activity of arcuate nucleus neurons over the light dark cycle, it also receives information about the feeding state of the animal. Additionally, both SCN and arcuate nucleus influence activity in the medial preoptic area to change the temperature set point (Guzman-Ruiz et al., 2015) (Fig. 1). This exchange of circadian, metabolic and temperature information at three anatomically distinct places, is necessary to adjust the temperature set point to different environmental conditions and is an example of how feedback to the SCN, provides an evolutionary advantage to survive unfavorable conditions. Another example is the anticipatory drinking that takes place before animals go to sleep, here, the interaction between the SCN and the OVLT has been shown to be essential (Gizowski et al., 2016). Perhaps the most striking example of the importance of feedback to the SCN is its evident reduction of neuronal activity, during day time restricted feeding in rats. In this experimental condition, animals receive food just for 2 h in their sleeping period. Thus making it essential for the animal to anticipate the arriving food, this anticipation is permitted by a reduction of the normally high neuronal activity of the SCN. This is enabled by a strong neuronal activation of the DMH that inhibits SCN activity. This allows the animal to become active prior to food presentation (Acosta-Galvan et al., 2011). Interestingly, several studies have shown that this experimental protocol does not influence the rhythm or phase of the SCN, this food anticipatory network, just adjust for some time the output of some SCN neurons.

These examples illustrate how neurons of the SCN receive information about the state of the organism, and adjust the physiology of the body through interactions with various areas of the CNS. They also illustrate and indicate how inputs that are not aligned with the output of the SCN clock (e.g., food intake or activity in the sleep phase) can be disruptive to normal function. Such disruptive inputs can, via feedback to the SCN, adjust the SCN neuronal output so that an animal's physiology can adjust successfully in relation to the time of the day. Therefore, shiftwork or other “stressors” give set point changing inputs to the SCN and thus, in the long term, may lead to pathology.

6. Live in the light and sleep in the dark

This is how evolution has prepared human beings for their survival on earth. However, the ability of humans to be active and eat outside the preferred period set by the SCN, is a behavioral adaptation that been greatly (over)exploited in modern living. Shift work, eating at night, being active associated with light exposure at night, intercontinental travelling, etcetera, are important elements of our modern life style. Such disruptions of our natural circadian rhythm have been associated with an increase in diseases such as depression, hypertension, obesity and diabetes. The consensus that this is due to disruption of our biological clock seems to be endorsed by the awarding of the 2017 Nobel Prize in medicine and physiology to three researchers who made seminal contributions to the discovery of the molecular mechanisms of the biological clock (Callaway and Ledford, 2017). The details of why constant disruption of the circadian clock is associated with an increased risk of these diseases is unclear. However, animal studies show, that eating in the sleep phase induces accumulation of fat in the liver together with the development of obesity (Salgado-Delgado et al., 2013). This aligns with epidemiological analysis of a 6-year survey among 2000 workers revealing a correlation between such pathologies and irregular eating, snacking habits, and insufficient hours of sleep (Imaki et al., 2002). Furthermore, nocturnal eating leads to an abnormal endocrine response (Holmback et al., 2003). Interestingly other studies show that overeaters tend to consume a larger part of their daily energy in the evening (Keim et al., 1996) and recently this has be show to be associated with an increased incidence of obesity (Panda, 2016). Disruption of the normal circadian cycle may also be the mechanism, and explain why insufficient sleep is associated with hypertension, obesity and diabetes (Gangwisch et al., 2006; Gangwisch et al., 2007). Explanations for these phenomena are often sought in changes to clock gene expression in peripheral organs and associated changes in metabolic enzymes. However, given the existing feedback mechanisms to SCN via both cranial and spinal afferents, and other

sensing areas of the brain, we consider it likely that not just peripheral processes account for these changes, but that the initial disturbance might be, the out of phase feedback to the SCN circadian clock. How aberrant interactions between SCN and other CNS structures and the periphery results in a fatty liver and in insulin insensitivity is still not well understood. We proposed (Kreier et al., 2003) that this may result in a deleterious adaptation of the output of the SCN, shifting autonomic and endocrine balance, which may result in pathophysiology; e.g., resulting in an imbalance of the autonomic nervous system culminating in intraperitoneal and liver fat deposits and shifts in cardiovascular control both associated with the metabolic syndrome and diabetes (Peterson et al., 1988). In support of this hypothesis, are the observations that in human conditions of hypertension and diabetes, SCN and SCN-controlled structures are notably affected (Goncharuk et al., 2001; Saderi et al., 2012) indicating that indeed the SCN could be a centerpiece in these pathologies. Goncharuk et al. (2001) observed in post mortem studies that persons whom passed away after a long history of hypertension had a strongly reduced activity of the SCN, and increased CRH staining in the PVN, indicating severe hypothalamic changes. The presence of SCN projections to the PVN and not the reverse, also in humans (Dai et al., 1998), and the strong correlation between decreased SCN activity and decreased PVN-CRH activity, indicates that a diminished SCN activity might be the basis of the pathology. In addition a strong increased activity of NPY neuronal activity in the postmortem arcuate nucleus of diabetes patients was observed (Saderi et al., 2012) also indicating that glucose sensing structures in the human diabetic brain can be affected. Since NPY in the arcuate nucleus is up regulated in fasted rats with low glucose levels, the observation of high NPY immunoreactivity in the arcuate nucleus of diabetic patients, suggests that in spite of their high glucose levels, the patients are not able to detect this.

In conclusion, animal studies indicate that both SCN and arcuate nucleus and their interaction play, an essential role in maintaining a balance in metabolism and ANS output. The observation in human studies that metabolic and ANS pathology is associated with changes in SCN and arcuate nucleus suggests that indeed a life style that disrupts metabolic and autonomic balance may lead to failure of these structures to respond adequately to the challenges of modern life.

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