Circadian Control of Neuroendocrine Systems

11

Ruud M. Buijs, Eva Soto-Tinoco, and Andries Kalsbeek

Abstract

Neuroendocrine systems together with the autonomic nervous system serve to synchronize physiological processes that keep the body in balance with the environment. Such a process, also called homeostasis, often is thought to keep the conditions in the body constant in a changing environment. The present paper discusses how the brain controls hormone secretion and how the suprachiasmatic nucleus(SCN), the brain's biological clock, influences this process, illustrating that the internal conditions are far from stable but vary with a precise daily rhythm. As a result of this, hormone levels may vary by a factor 10 or more over the day–night cycle, but at a given hour may vary by less than 5% from 1 day to another. Clearly, the SCN influences a vast neuronal network within the hypothalamus, thus controlling a circadian rhythm in hormone secretion. These changing levels in circulating hormones need to be carefully tuned with the autonomic output to the organs to achieve the optimal physiological conditions needed at that time point. Particular emphasis will be paid to the rhythms of melatonin, corticosterone, and luteinizing hormone, of which the last one, even though in rats it only occurs once every 4–5 days, is also driven by the SCN. Finally, attention will also be given to the need of the SCN to be informed about the actual circulating concentration of the hormones, in order to adjust the hormonal levels to the levels appropriate to the time of the day.

R. M. Buijs (✉) · E. Soto-Tinoco
Department of Cellular Biology and Physiology, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad de Mexico, Mexico
e-mail: buijs@iibiomedicas.unam.mx

A. Kalsbeek
Department of Endocrinology and Metabolism, Amsterdam University Medical Centers (UMC), Location AMC, Amsterdam, The Netherlands

V. Grinevich, Á. Dobolyi (eds.), *Neuroanatomy of Neuroendocrine Systems*, Masterclass in Neuroendocrinology 12,
https://doi.org/10.1007/978-3-030-86630-3_11

Keywords

Suprachiasmatic nucleus · Melatonin · Corticosterone · Luteinizing hormone · Autonomic nervous system · Circadian

11.1 Introduction

A neuroendocrine system can be defined as a group of neurons that produce the same hormone and release that hormone into the circulation under the influence of other brain areas. A target of a neuroendocrine system is defined as any structure in the body that expresses the adequate receptors for the released hormone. These receptors can be located in many tissues of the body or may be present only in other endocrine organs, such as the anterior pituitary. Consequently, the result of the activation of these neuroendocrine systems is the liberation of hormones that, directly or indirectly, influence various functions in the body. The neuroendocrine systems we will discuss in the present chapter are hypothalamic systems that release their hormones directly into the circulation, either via the median eminence or via the pituitary neural lobe.

Classical hormones released from peripheral tissues, such as insulin, adrenalin, and cholecystokinin, respond either to circulating factors, to other hormones or to tissue-specific stimuli. Meanwhile, neuroendocrine systems are directly influenced by many brain regions and respond to neuronal stimuli resulting from emotions or stimuli from the body sensed by the brain. In this chapter, however, we will pay special attention to the circadian system since it is a unique brain system that influences all, or nearly all, neuroendocrine systems.

Since it is essential for preparing the body for the daily cycle of activity and inactivity, the circadian system is of great importance for all neuroendocrine systems. As indicated before, the hormones of the neuroendocrine systems are essential for adapting the organs of the body for their functions; therefore, the activity-inactivity cycle is one of the main determining variables that requires different levels of hormonal action. These different levels of hormonal action can be obtained by changing hormone concentrations and receptor sensitivity. As we will see for many hormones, both possibilities take place.

Considering that the Suprachiasmatic Nucleus (SCN), the master clock that synchronizes our behavior with the light–dark cycle, activity changes such as food and fluid intake may influence several hormonal rhythms. In the present chapter, we will not take into consideration these behavior-induced hormonal changes, but instead, we will pay attention to hormonal changes that are directly influenced or induced by the SCN.

11.2 The Circadian System

The circadian system comprises the central biological clock, the suprachiasmatic nucleus (SCN), located at the base of the hypothalamus, as well as numerous peripheral clocks located in other brain areas and peripheral tissues. The SCN is constituted of approximately 20,000 neurons, accompanied by glial cells, that have an endogenous activity rhythm. Recent studies have demonstrated that the unique ability of the SCN to generate and sustain an autonomous rhythm, even in vitro, depends not only on the interaction of the different neuronal populations with each other but also on their interaction with the glial cells in the SCN (Brancaccio et al. 2019; Freeman and Herzog 2011).

The release of SCN neurotransmitters into target areas in the hypothalamus transmits the rhythm in neuronal activity to brain areas involved in the control of behavior and different neuroendocrine functions. These hypothalamic projections allow the SCN to influence all aspects of body homeostasis by synchronizing behavior with the functionality of the organs via autonomic and hormonal outputs.

The hypothalamic location of the SCN provides another functional advantage. Positioned just above the optic chiasm, the SCN receives direct light input from the retina, allowing it to synchronize its endogenous circadian rhythmicity with the exact 24 h period of the environmental light–dark cycle (Jones et al. 2018). This synchrony is essential because the daily change in light and darkness is the only reliably constant in the universe and thus, the main synchronizer of all activity.

However, optimal synchronization cannot take place without the SCN being informed about the actual situation in the body. The SCN has been shown to have extensive reciprocal contacts with several brain areas, with afferent connections informing the SCN about the actual physiological conditions of the body. This feedback information results in an adaptation of the output of the SCN (via its efferent projections), that accommodates the physiology to meet the particular needs of the body at any given time of the day (Buijs et al. 2017, 2019).

For example, the SCN has a reciprocal interaction with the arcuate nucleus, also located in the hypothalamus. The arcuate nucleus is an important circumventricular organ that receives information from the circulation via the median eminence, which possesses fenestrated capillaries. This characteristic places the arcuate nucleus, as well as the other circumventricular organs, in a privileged position, allowing them to continuously monitor circulating information (Gropp et al. 2005; Dietrich et al. 2015; Buijs et al. 2017).

The interaction between the SCN and the arcuate nucleus is essential for organizing the daily rhythm in body temperature, which is strongly associated with the animal's metabolic conditions. On the one hand, the SCN imposes a rhythm on the activity of arcuate α-MSH neurons, whose activity is essential for maintaining a high temperature at the end of the activity phase. On the other hand, vasopressin (VP) projections from the SCN to one of the primary brain areas involved in temperature regulation, the medial preoptic area, are essential for the decrease in temperature at the beginning of the sleep phase (Guzmán-Ruiz et al. 2014, 2015). A more pronounced drop in temperature only at the beginning of the inactive period

occurs under fasting conditions. This temperature drop depends on the presence of the SCN; without the SCN, the temperature remains high at any given time of the circadian cycle, even under fasting conditions (Liu et al. 2002). This observation, together with the data showing that SCN-VP is essential for the temperature drop in the early day period, indicates that the fasting information needs to reach the SCN. Therefore, the connection with the arcuate nucleus is the most logical underlying anatomical basis for the transmission of metabolic information to the SCN (Buijs et al. 2017).

11.3 Rhythmic Secretion of Melatonin: A Reflection of SCN Activity

Several hormones show a precise circadian rhythm directly driven by SCN neuronal activity. For example, melatonin secretion is directly induced by the neuronal activity of glutamatergic SCN neurons connected with pre-autonomic neurons in the paraventricular nucleus (PVN), which, via autonomic sympathetic output, drives melatonin secretion from the pineal gland (Teclemariam Mesbah et al. 1999; Perreau-Lenz et al. 2004) (Fig. 11.1). Surprisingly, these glutamatergic SCN neurons are always active and provide a constant stimulus for melatonin secretion. Nevertheless, we know that even in constant-dark conditions, melatonin secretion occurs only in the subjective dark period, earning the name "the hormone of darkness." This raises the question of what are the exact mechanisms for the stimulation and inhibition of melatonin secretion. A series of studies by Perreau-Lenz et al. (2004,

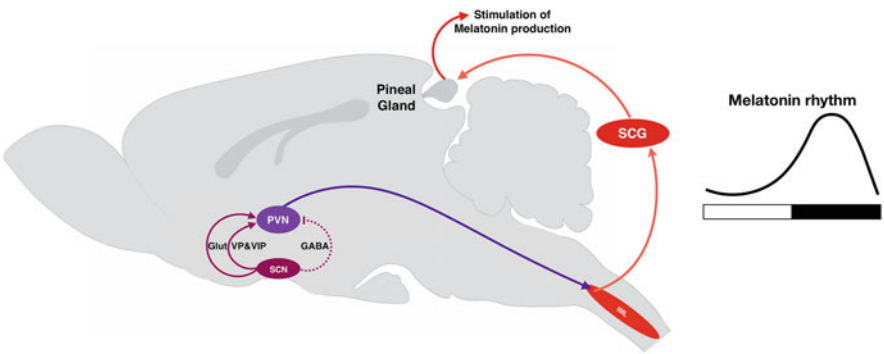

Fig. 11.1 Circadian control of melatonin secretion. Glutamatergic (Glut) projections from the SCN constantly stimulate a specific set of pre-autonomic neurons in the paraventricular nucleus of the hypothalamus (PVN). Vasopressin (VP) and Vasoactive Intestinal Peptide (VIP) also have a stimulatory effect over these pre-autonomic neurons in the PVN. Specifically, these PVN neurons are connected with sympathetic motor neurons located in the intermediolateral column (IML) of the spinal cord, that project to the superior cervical ganglion (SCG). Sympathetic postganglionic noradrenergic neurons projecting to the pineal stimulate the release of melatonin. During the day or subjective day, GABAergic projections from the SCN are activated and override the stimulatory input to the pre-autonomic neurons in the PVN, thereby preventing the melatonin release

2005) showed that these pre-autonomic PVN neurons also receive input from GABAergic SCN neurons, and their light or subjective day-induced inhibitory activity prevents the activation of the sympathetic output to the pineal. Therefore, the rhythm of these GABAergic neurons is essential for rhythmic melatonin secretion. This "simple" control of melatonin secretion might be related to the fact that melatonin is not (or only very little) influenced by other hormones or behaviors in all organisms. Consequently, these observations indicate that a diminution of nightly melatonin secretion could be almost completely ascribed to a decreased activity of the SCN's glutamatergic neurons. Such diminished melatonin secretion is, for example, observed in older people and people with Alzheimer's disease (Mirmiran et al. 1989; Uchida et al. 1996), indicating a lower activity of the glutamatergic neurons of the SCN. This concurs with the diminished SCN activity found in *post mortem* hypothalamic tissue of these subjects (Swaab 2004).

In this regard, it is interesting that melatonin secretion is also diminished in people with hypertension (Brugger et al. 1995; Zeman et al. 2005), indicating that high blood pressure may also interfere with SCN neuronal activity. This idea was corroborated in a study that evaluated *post mortem* tissue from hypertensive people and observed substantial reductions in SCN neuronal activity (Goncharuk et al. 2001).

In search of further mechanistic explanations for those observations, we demonstrated in rodents that the SCN is sensitive to increases in blood pressure (BP) (Buijs et al. 2014; Romo-Nava et al. 2017; Yilmaz et al. 2018, 2019). The nucleus of tractus solitarius (NTS) transmits information about BP increases directly to the SCN. This feedback serves to reduce BP to normal levels, which are determined by the time of the day. A clear illustration of the importance of the SCN in the control of BP is that when a stressful stimulus is given to an SCN lesioned animal, there is an exacerbated increase in BP compared to a sham-operated animal (Buijs et al. 2014; Romo-Nava et al. 2017).

The observations that hypertensive and obese people have a more disturbed sleep–wake pattern than non-hypertensive people (Gangwisch et al. 2005, 2006) provides further support for the hypothesis that alterations in our biological clock might be at the core of the recent surge in diabetes and hypertension (Kreier et al. 2003). In agreement, it was recently shown that the *post mortem* brains of type 2 diabetes patients also show the diminished activity of the SCN (Hogenboom et al. 2019). Together, these observations raise the question of whether these SCN changes in the *post mortem* hypertensive or diabetic human brain are a cause or consequence of hypertension and diabetes. Disturbed sleep–wake rhythms in these patients, together with the above-detailed observations that the SCN is sensitive to feedback, suggest that behavioral changes, and consequently changes in physiology, may be responsible for the observed alterations in the SCN. Considering that, as shown above, the biological clock plays an essential role in determining the setpoints of our physiology, any long-term disturbance in the activity of the SCN may have severe repercussions for our health. Recent shifts in human behavior, such as being active and eating during the night and the resulting changes in the SCN, may start a

vicious downward spiral. Therefore, we emphasize that changes in our behavior that are incompatible with the signals of the SCN may result in disease.

The studies mentioned above indicate that disturbances in SCN neuronal activity induced by aging, disease, medicines or other factors may, in the long term, result in important deviations from the normal physiology. However, the good news is that changes in the patient's physiology due to side-effect action of medicines on the SCN may be reversed by melatonin 'treatment'. An example of this is the second-generation antipsychotic (SGA) Olanzapine that is associated with adverse cardio-metabolic side effects that contribute to premature mortality in patients (Lieberman et al. 2005). Surprisingly enough, melatonin treatment in patients taking SGAs largely diminished these side effects, while maintaining the beneficial effects of the SGAs (Romo-Nava et al. 2014). In animal studies, initiated to find a mechanistic explanation for this observation, it was shown that Olanzapine activates areas of the limbic system as well as the SCN. Through this SCN activation, the hypothalamic output to the parasympathetic system is activated (Romo-Nava et al. 2017).

The selective coordination of the autonomic nervous system in different compartments of the body is an important output mechanism of the SCN (Kreier et al. 2002, 2006) and alterations of this output may, in time, promote the development of the metabolic syndrome (Kreier et al. 2003). In this regard, even with short-term Olanzapine treatment, the parasympathetic activation induces adiposity and increases circulating adiponectin (Togo et al. 2004). Consequently, the increased parasympathetic activity induced by Olanzapine favors the appearance of adverse cardio-metabolic effects such as obesity and changes in plasma lipids, insulin, and glucose (Lieberman et al. 2005). These disturbances are similar to those observed in the metabolic syndrome, where in the long term a compensatory increase in sympathetic cardiovascular tone gives rise to hypertension. However, the observed activation of the SCN by Olanzapine in rats is effectively prevented by treating these animals with melatonin (Romo-Nava et al. 2017), in line with the well-known inhibitory effect of melatonin on SCN activity. In agreement, two other studies also showed that melatonin mitigated Olanzapine-induced cardio-metabolic effects in patients diagnosed with schizophrenia and bipolar disorder (Modabbernia et al. 2014; Mostafavi et al. 2014).

11.4 Corticosterone

The secretion of cortisol in humans and corticosterone in rodents shows a precise circadian rhythm, with higher circulating levels anticipating the activity period. Despite what most handbooks still say, several studies have demonstrated that the circadian peak in corticosterone is not driven by adrenocorticotropic hormone (ACTH), but rather by the sympathetic innervation of the adrenal (Engeland and Arnhold 2005). This could already be deduced from the early studies of Berson and Yalow (1968), demonstrating that the blood levels of ACTH in humans hardly show a rhythm, in contrast to cortisol, which shows a high-amplitude rhythm. Similarly to humans, ACTH does not show a pronounced rhythm in rodents, indicating that the

direct sympathetic drive to the adrenal is responsible for the circadian peak in corticosterone, and making ACTH a permissive factor. Indeed, it has been shown that the corticosterone peak is driven by SCN neurotransmitters influencing the PVN pre-autonomic neurons that project to the sympathetic autonomic neurons innervating the adrenal gland (Buijs et al. 1999; Ishida et al. 2005; Kalsbeek et al. 1996).

Likewise, the stress response is under circadian control, with lower corticosterone responses to stressors presented at the beginning of the activity period and higher responses to stressors presented before the resting period (Buijs et al. 1993). However, different types of stressors can have different circadian patterns. For instance, a metabolic stressor in the form of a hypoglycemic stimulus (insulin) does not induce an increased corticosterone response at the beginning of the resting phase as high that observed after an emotional stressor (a new cage). In the beginning of the active phase, the reverse happens, with a low corticosterone response after the stress of a new cage and a high corticosterone response after the hypoglycemia-induced stress (Kalsbeek et al. 2003). These observations show the complexity (and logic) of the influence of the circadian system on the neuroendocrine responses. Moving into a new cage early in the sleep phase is more disturbing than when it occurs at the beginning of the active phase; thus, it evokes a higher corticosterone secretion. On the other hand, hypoglycemia is more disturbing when being active than when being inactive; hence, it evokes a higher corticosterone response in the active period.

Several observations indicate that the SCN has an inhibitory role in the secretion of corticosterone. First, compared to intact animals, SCN-lesioned animals respond with much higher corticosterone levels when challenged with a stressor. Second, compared to intact animals, SCN-lesioned animals show much a higher basal corticosterone level (Buijs et al. 1997; Kalsbeek et al. 2003). However, the circadian peak of corticosterone in intact animals is higher than the levels in undisturbed SCN-lesioned animals, indicating that the SCN also has a stimulatory influence on corticosterone secretion (Kalsbeek et al. 1996).

Which SCN transmitter is responsible for this stimulation of corticosterone secretion has not been determined. However, the inhibitory influence of the SCN on corticosterone secretion is mediated by the VP neurons of the SCN. The release of VP from the SCN starts at ZT18 and it peaks at ZT6, and thereafter VP release decreases (Schwartz and Reppert 1985). This VP release from SCN terminals at pre-autonomic neurons of the PVN is responsible for inhibiting corticosterone secretion (Fig. 11.2); a timed infusion of VP antagonists demonstrated that only early day infusions of the antagonist could increase corticosterone levels. In agreement with its release pattern, VP only inhibits corticosterone secretion in the early light period (Kalsbeek et al. 1996).

This study also revealed a stimulatory SCN input that exists only from the end of the activity period until the end of the light period. The interaction between the unknown stimulatory SCN input and the VP inhibitory input shapes the circadian peak in corticosterone (Kalsbeek et al. 1996). Recent studies indicate that the unknown stimulatory input could be the SCN Vasoactive Intestinal Peptide (VIP)

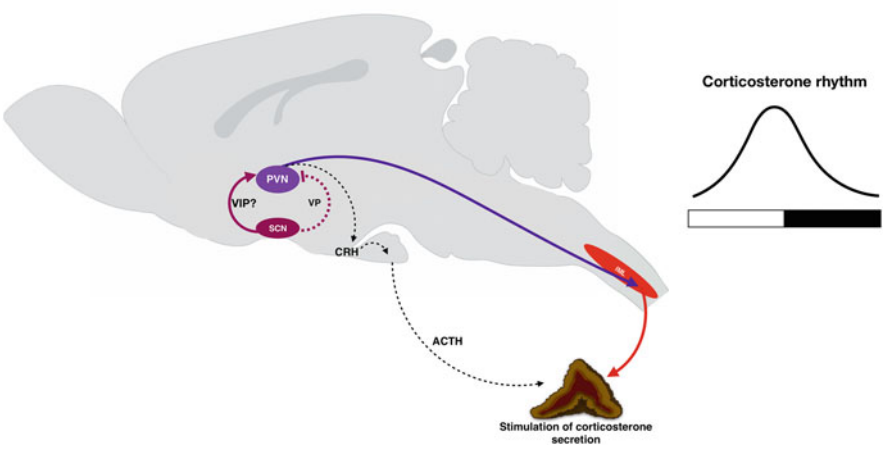

Fig. 11.2 Circadian control of corticosterone secretion. Vasopressin (VP) and other (VIP?) neurons from the Suprachiasmatic Nucleus (SCN) project to pre-autonomic neurons in the paraventricular nucleus of the hypothalamus (PVN). These pre-autonomic neurons project to the sympathetic motor neurons located in the intermediolateral column (IML) of the spinal cord that project to the adrenal and stimulate corticosterone secretion (and are thus different from those that stimulate melatonin secretion). An unknown stimulatory input from the SCN (VIP?) activates those pre-autonomic neurons, resulting in the peak of corticosterone secretion just before the activity period. In addition, Corticotrophin Releasing Hormone (CRH) is produced in the PVN and is released into the median eminence to reach the anterior pituitary, where it stimulates the release of adenocorticotropic hormone (ACTH) into the circulation. The occupation of ACTH receptors in the adrenal cortex is necessary to obtain corticosterone release by the adrenal cortex. From other brain areas, there are also stimulatory inputs to the PVN provoking corticosterone secretion. VP released from SCN terminals strongly inhibits these adrenal connecting pre-autonomic neurons in the PVN during the early morning, resulting in very low corticosterone levels

neurons (Mazuski et al. 2020), suggesting that the activity of those VIP neurons should be high from the middle of the light period to the beginning of the dark period.

11.4.1 Corticosterone Negative Feedback

To adjust the circulating level of corticosterone, it is essential to precisely monitor its concentration and transmit this information to the brain areas involved in releasing ACTH and corticosterone. How circulating corticosterone may enter the brain is still under discussion. However, there is some evidence that in the blood–brain barrier (BBB), multidrug resistance P-glycoprotein (MDR) plays a role in transporting corticosterone into the brain (Karssen et al. 2001).

The negative feedback of corticosterone is proposed to occur at the PVN level, where Corticotrophin Releasing Hormone (CRH) neurons control the secretion of ACTH from the pituitary. These CRH neurons express glucocorticoid receptors (GR) and diminish their activity and CRH production under the influence of

glucocorticoids. However, as we have seen, the control of glucocorticoid secretion occurs mainly via the activation of pre-autonomic neurons in the PVN projecting to the adrenal. These neurons do not express GR and thus are not directly sensitive to glucocorticoid feedback (Leon-Mercado et al. 2017). Moreover, since glucocorticoids do not easily penetrate the BBB, the question is: If there is a fast release of corticosterone, is there also a fast feedback?

To answer this question, we need to focus our attention on those areas where the brain can rapidly monitor the circulating concentration of corticosterone: the four sensory circumventricular organs (CVOs), which possess a more permissive BBB. These structures are the Organum Vasculosum of the Lamina Terminalis (OVLT), the Subfornical Organ (SFO), the Median Eminence (ME)-Arcuate nucleus complex (ARC), and the Area Postrema (AP). The OVLT and SFO are mainly involved in the surveillance of the mineral balance of the body (Gizowski et al. 2016; Gizowski and Bourque 2020; Mimee et al. 2013), whereas the ME-ARC and AP are important for monitoring the metabolic condition (Langlet et al. 2013; Larsen et al. 1997).

Two of the CVOs, the OVLT and ME-ARC, have extensive reciprocal interaction with the SCN, while for the SFO and AP, this has not been demonstrated, but all have elaborate connections with the PVN. Of these four CVOs, only the ARC has a high concentration of GR, making it the logical candidate for corticosterone's fast feedback upon its secretion from the adrenal. Using microdialysis probes inside the ARC and infusing specific GR and mineralocorticoid receptor (MR) agonists and antagonists at different times of the day, it was demonstrated that when systemic corticosterone levels are low, the *MR* has a vital role in the negative feedback. In contrast, when circulating corticosterone concentrations are high, the *GR* is essential for negative feedback. Notably, the increase or suppression in circulating corticosterone levels by MR or GR (ant)agonists in the ARC took place without any change in circulating ACTH (Leon-Mercado et al. 2017), confirming that the hypothalamic output to the adrenal via the ANS executed those changes. This observation illustrates that the brain's CVOs play a crucial role in sensing circulating molecules and signal those levels to regulatory centers in the brainstem and hypothalamus, to adjust not only metabolic conditions but also hormonal levels.

11.5 Luteinizing Hormone

Probably for no other hormone, the timing of secretion is so crucial as that for the Luteinizing Hormone (LH). In addition, perhaps no other hormone is under the influence of so many different factors as the LH. In rodents, there is extensive experimental evidence that the SCN drives the preovulatory LH release, while there is also preliminary evidence that this SCN action is accompanied by its simultaneous influence on the ovary via the autonomic nervous system to induce ovulation (Silva et al. 2020). The involvement of the SCN in the LH surge was first indicated by Everett and Sawyer, who were able to postpone the LH surge in female rats by 24 h with an injection of Nembutal, provided that the injection was given at a crucial moment before ovulation. This pioneering study indicated the circadian

control of ovulation (Everett and Sawyer 1950). Legan and Karsch (1975) provided another piece of evidence when they showed that ovariectomized-estrogen-treated animals show a surge in LH every day (Legan and Karsch 1975), instead of only once every 4–5 days. These experimental conditions also provide an excellent experimental model in which to study how the SCN can influence LH secretion.

In addition to the gonadotrophin-releasing hormone (GnRH) neurons and the circadian system, several other systems are involved in the daily control of LH secretion. Ovulation takes place once every 28 days in humans, raising the question of whether the SCN is still involved in the organization of the menstrual cycle. Despite the monthly cycle, much evidence indicates that similar mechanisms of control exist for human ovulation. Spontaneous initiation of the preovulatory LH surge in women generally occurs in the morning together with the cortisol peak, indicating the importance of the SCN in the timing of human ovulation (Cahill et al. 1998; Kerdelhue et al. 2002).

The SCN involvement in the control of human ovulation was challenged by the observation that the amplitude and frequency of pulsatile LH secretion did not vary over a 24 h period in premenopausal women studied under constant laboratory conditions (Klingman et al. 2011). However, the conditions used in this study, constant light and constant activity for 32 h, could be enough to disrupt the ovulatory cycle (Scarinci et al. 2019). For instance, the ovulatory cycle is modulated by melatonin and melatonin secretion certainly will be disrupted by the constant light conditions used in that study. Moreover, women living under normal LD conditions were lacking as controls, meaning that very little can be concluded from this study.

The complexity of the LH surge timing becomes evident when we consider the contribution of different SCN neuronal populations to the ovulatory cycle. SCN-VP neurons project to the medial preoptic area, where (even in SCN-lesioned animals) VP infusion can induce an LH surge (Palm et al. 1999). Moreover, in SCN-intact, but ovariectomized, estradiol-treated animals, VP could induce this LH surge only within a specific time window (Palm et al. 2001). Both studies show the importance of VP stimulation for the LH surge. After discovering a Kisspeptin population in the medial preoptic area, it became clear that the SCN-VP projections to these Kisspeptin neurons (Vida et al. 2010) underlie the effects of VP on LH secretion (Fig. 11.3).

Besides the influence of VP, Vasoactive Intestinal Peptide (VIP) neurons of the SCN are also involved in controlling the LH surge. The SCN-VIP neurons directly project to GnRH neurons located in the rostral medial preoptic area (Van Der Beek et al. 1997). These VIP neuronal terminals preferentially appose GnRH neurons that show activation (measured by c-Fos) during an LH surge (Van Der Beek et al. 1994). In agreement with this, the LH surge is diminished or prevented by an injection of VIP antiserum (which neutralizes the effects of VIP) (Van Der Beek et al. 1999). Therefore, just like the VP neurons, the VIP projections from the SCN serve to stimulate the GnRH neurons. The timing between the activation of these two neuronal populations is probably essential for an accurate control of ovulation. Moreover, also prokineticin neurons in the SCN may be involved in controlling

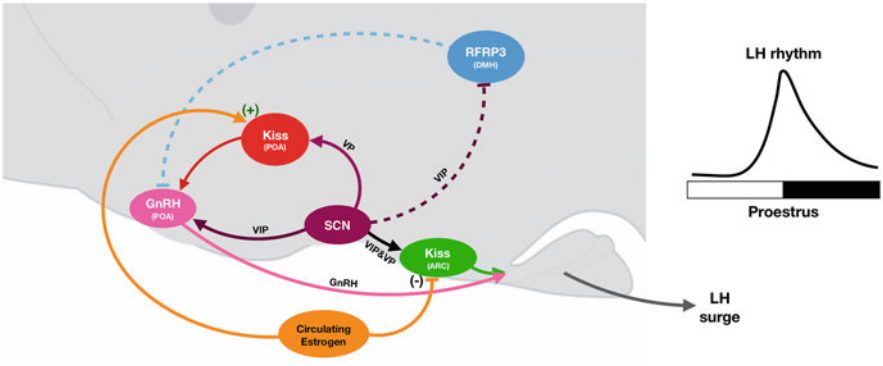

Fig. 11.3 Circadian control of the LH surge. At the center, the suprachiasmatic nucleus (SCN) has projections to several neuronal populations important for the LH surge. With vasopressin (AVP) it stimulates Kisspeptin (Kiss) neurons in the medial preoptic area (POA). With VIP it stimulates Gonadotropin-Releasing Hormone (GnRH) neurons in the POA, while inhibiting RFamide-related peptide 3 (RFRP3) neurons in the dorsomedial hypothalamus (DMH). With both, VIP and AVP, the SCN targets Kiss neurons in the arcuate nucleus (ARC). Kiss neurons in the POA stimulate GnRH neurons in the POA for the release of LH, while RFRP3 neurons inhibit GnRH neurons, and therefore prevent the LH surge. The SCN inhibits the inhibition of the RFRP3 neurons over the GnRH neurons, allowing the LH surge to take place. Lastly, circulating estrogen modulates both populations of Kiss neurons in opposite ways, activating the POA population while inhibiting the ARC population. Just before ovulation, the estrogen levels drop, resulting in an increase of Kisspeptin activity in the ARC which promotes, via its terminals in the median eminence, the final activation of GnRH terminals for the release of LH

the LH surge since receptors for this peptide are present on estradiol-activated neurons in the medial preoptic area (Xiao et al. 2014).

Apart from daily rhythms, other conditions influence the LH surge, such as seasonal or metabolic influences. The seasonal influence on reproduction will hardly play a role in most humans, except when we consider the shortage of food, which may be strongly seasonal in some cultures. On the other hand, many studies illustrate how metabolic conditions play an important role in the functioning of the reproductive cycle. In these studies, the arcuate nucleus appears as an important brain area able to influence the LH surge. As mentioned before, the arcuate is involved in monitoring the metabolic state of the animal via the sensing of circulating metabolites. Arcuate nucleus kisspeptin neurons, Agouti-related peptide (AgRP) and Pro-opioid Melanocortin (POMC) neurons project to the medial preoptic area (MnPO), to the dorsomedial nucleus of the hypothalamus (DMH) and to the PVN (Padilla et al. 2019), all of which structures are involved in the processing of reproductive and metabolic information.

As described above, the arcuate has bidirectional connections with the SCN that are essential for the organization of many circadian rhythms (Yi et al. 2006; Buijs et al. 2017). Such reciprocal connections also exist between the DMH and the SCN (Acosta-Galvan et al. 2011), demonstrating the importance of the interaction between time and metabolism. Furthermore, several physiological studies have

shown the importance of the interaction of the SCN, arcuate and DMH with the medial preoptic area, and emphasized the importance of these areas for controlling reproduction and temperature regulation (Buijs et al. 2017; Guzmán-Ruiz et al. 2015; Padilla et al. 2019).

The SCN and arcuate coordinate the diurnal temperature decrease in the MnPO. The MnPO receives SCN and ARC efferents that influence the temperature. During the night, an SCN-mediated activation of arcuate nucleus α-MSH neurons (Guzmán-Ruiz et al. 2014) sustains high body temperature during the night. In the last part of the dark phase, vasopressin is released from SCN terminals, having a hypothermic effect in the MnPO. This hypothermic effect of vasopressin is counteracted by α-MSH activity in the arcuate as long as it is night. At the onset of the light phase, the SCN inhibits the activity of the arcuate α-MSH neurons (Guzmán-Ruiz et al. 2014). Without α-MSH thermogenic counteraction, vasopressin is able to exert its hypothermic effect and the temperature drops at the beginning of the light period. For more details see Guzmán-Ruiz et al. (2015).

Interestingly, Kisspeptin neuronal populations located in both the medial preoptic area and arcuate nucleus are strongly under the influence of the gonadal hormones estrogen and testosterone. These steroid hormones strongly stimulate Kisspeptin production in the neurons of the medial preoptic area, while inhibiting the production of Kisspeptin in the arcuate nucleus (Smith et al. 2006). Interestingly, both kisspeptin populations have an important stimulatory role on LH secretion (Estrada et al. 2006), indicating that estrogen changes just before ovulation also need to be timed precisely, making the SCN control of the autonomic innervation of the ovary essential. This may be reflected in the way both populations of Kisspeptin neurons influence the GnRH neurons: the medial preoptic area Kisspeptin population mainly influences the GnRH cell bodies, while the arcuate population is better positioned to influence the GnRH axons terminating in the median eminence (Matsuyama et al. 2011; Yip et al. 2021). This suggests that when estrogen levels drop just before ovulation, the Kisspeptin arcuate neurons are stimulated, which then stimulates the GnRH terminals for the final release to induce the LH surge (Fig. 11.3). In addition, this decrease in estrogen and the consequent increase in Kisspeptin activity in the arcuate may also account for the temperature increase after ovulation. It has been demonstrated that the activity of arcuate Kisspeptin-Neurokinin B neurons induces an excess release of Neurokinin B in the medial preoptic area, leading to the activation of the parasympathetic outflow to the blood vessels of the skin, which results in vasodilation and the feeling of hot flushes (Padilla et al. 2018; Rometo et al. 2007; Mittelman-Smith et al. 2012a, b). The same neurons are also important for the control of metabolism (Padilla et al. 2019); again, evidencing a tight coupling between temperature, reproduction, and metabolism.

A similar interaction occurs between the SCN and the DMH, which is also an area where circadian, metabolic, and temperature information is integrated. Here, another population of RF-amide neurons, RFRP-3 (RF-amide-related peptide 3), regulates GnRH neuron activity and gonadotropin secretion. RFRP-3 is known to exert an inhibitory role over the GnRH signaling, although that depends on the species studied.

In female Syrian hamsters (*Mesocricetus auratus*), RFRP-3 neurons have close appositions with SCN derived VP and VIP fibers (Russo et al. 2015, 2018), suggesting that the SCN could also be involved in coordinating the inhibitory functions of RFRP-3 neurons. Indeed, VIP suppresses RFRP-3 neuronal activity only when injected in the evening, therefore removing its inhibitory influence over the GnRH neurons. Together, these data indicate that the SCN can stimulate GnRH secretion by direct projections to the GnRH neurons and indirectly through the inhibition of RFRP-3 neurons, both actions carried on by VIP projections (Russo et al. 2015, 2018). These examples illustrate that the SCN orchestrates the optimal timing of such an important event as ovulation via multiple targets. Moreover, the SCN-VIP neurons receive dense input (feedback) from the DMH-RFRP-3 neurons (Acosta-Galvan et al. 2011) that is essential for the organization of locomotor activity of the animal, which is another behavior that shows profound changes around ovulation in many animal species.

In addition, since there are multi-synaptic connections from the SCN to the ovary (Gerendai et al. 2000) and disruption of the autonomic output to the ovaries disrupts the onset of ovulation (Ramírez et al. 2017), it is likely that the SCN is also involved in the additional autonomic control of ovulation. (Buijs and Kalsbeek 2001)

11.6 Conclusion/Perspective

These examples illustrate the extensive possibilities of the SCN to modulate/influence essential physiological functions of the body. It is established that the SCN employs a wide network of hypothalamic systems that influence the secretion of hormones to target the organs of the body. However, these hormonal actions on the organs are far from sufficient. Therefore, via the same hypothalamic systems, the SCN also changes the autonomic output, thus targeting neuronally the same organs that are reached by circulating hormones. The apparent need of the SCN to influence and synchronize these two systems indicates the urgency for a better understanding of their interaction, not only because it gives a better understanding of how the SCN can synchronize functions in our body, but more because it is essential to understand how the autonomic nervous system sensitizes our organs for the circulating hormones.

Acknowledgments This work was supported by the Dirección General de Asuntos del Personal Académico Grant DGAPA IG-201321 and CONACyT QUEBEC 279293 (to R.M.B.).

Key References

Brancaccio M, Edwards MD, Patton AP, Smyllie NJ, Chesham JE, Maywood ES, Hastings MH (2019) Cell-autonomous clock of astrocytes drives circadian behavior in mammals. Science 363:187–192. https://doi.org/10.1126/science.aat4104. *Not only the neurons in the SCN, but also the glial cells, are essential for the autonomous rhythm*

Buijs RM, Guzmán Ruiz MA, Méndez Hernández R, Rodríguez Cortés B (2019) The suprachiasmatic nucleus; a responsive clock regulating homeostasis by daily changing the setpoints of physiological parameters. Auton Neurosci Basic Clin 218:43–50. https://doi.org/10.1016/j.autneu.2019.02.001. *Review of the need for feedback to the SCN in order to drive rhythmicity in physiology and behavior*

Kreier F, Kap YS, Mettenleiter TC, Van Heijningen C, Van Der Vliet J, Kalsbeek A, Sauerwein HP, Fliers E, Romijn JA, Buijs RM (2006) Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. Endocrinology 147:1140–1147. https://doi.org/10.1210/en.2005-0667. *Evidence for the presence of different neurons in the SCN projecting multisynaptiacally to different organs*

Kreier F, Yilmaz A, Kalsbeek A, Romijn JA, Sauerwein HP, Fliers E, Buijs RM (2003) Hypothesis: shifting the equilibrium from activity to food leads to autonomic unbalance and the metabolic syndrome. Diabetes. https://doi.org/10.2337/diabetes.52.11.2652. *One of the first papers to provide a mechanism for how shifted food intake patterns may lead to the metabolic syndrome*

Langlet F, Levin BE, Luquet S, Mazzone M, Messina A, Dunn-Meynell AA, Balland E, Lacombe A, Mazur D, Carmeliet P, Bouret SG, Prevot V, Dehouck B (2013) Tanycytic VEGF-A boosts blood-hypothalamus barrier plasticity and access of metabolic signals to the arcuate nucleus in response to fasting. Cell Metab 17:607–617. *An excellent demonstration of the importance of the arcuate nucleus for the transmission of metabolic information to the brain*

Leon-Mercado L, Chao DHM, Basualdo MC, Kawata M, Escobar C, Buijs RM (2017) The arcuate nucleus: a site of fast negative feedback for corticosterone secretion in male rats. eNeuro 4:1–14. https://doi.org/10.1523/ENEURO.0350-16.2017. *The first study to show the route for the fast feedback of corticosterone*

Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD (2018) A neural circuit underlying the generation of hot flushes. Cell Rep 24:271–277. https://doi.org/10.1016/j.celrep.2018.06.037. *A clear demonstration that Kisspeptin neurons serve not only for stimulating LH secretion but also for temperature regulation*

Romo-Nava F, Buijs FN, Valdés-Tovar M, Benítez-King G, Basualdo MC, Perusquía M, Heinze G, Escobar C, Buijs RM (2017) Olanzapine-induced early cardiovascular effects are mediated by the biological clock and prevented by melatonin. J Pineal Res 62:1–14. https://doi.org/10.1111/jpi.12402. *This study shows possible mechanisms of the induction of hypertension and obesity by antipsychotics and how the intake of melatonin may prevent that*

References

Acosta-Galvan G, Yi C-X, Van Der Vliet J, Jhamandas JH, Panula P, Angeles-Castellanos M, Del Carmen Basualdo M, Escobar C, Buijs RM (2011) Interaction between hypothalamic dorsomedial nucleus and the suprachiasmatic nucleus determines intensity of food anticipatory behavior. Proc Natl Acad Sci U S A 108:5813–5818. https://doi.org/10.1073/pnas.1015551108

Berson SA, Yalow RS (1968) Radioimmunoassay of ACTH in plasma. J Clin Invest 47:2725–2751. https://doi.org/10.1172/JCI105955

Brancaccio M, Edwards MD, Patton AP, Smyllie NJ, Chesham JE, Maywood ES, Hastings MH (2019) Cell-autonomous clock of astrocytes drives circadian behavior in mammals. Science 363:187–192. https://doi.org/10.1126/science.aat4104

Brugger P, Marktl W, Herold M (1995) Impaired nocturnal secretion of melatonin in coronary heart disease. Lancet 345:1408

Buijs RM, Kalsbeek A (2001) Hypothalamic integration of central and peripheral clocks. Nat Rev Neurosci 2:521–526. https://doi.org/10.1038/35081582

Buijs RM, Kalsbeek A, Van der Woude TP, Van Heerikhuize JJ, Shinn S (1993) Suprachiasmatic nucleus lesion increases corticosterone secretion. Am J Physiol Regul Integr Comp Physiol 264:33–36. https://doi.org/10.1152/ajpregu.1993.264.6.r1186

Buijs RM, Wortel J, Van Heerikhuize JJ, Kalsbeek A (1997) Novel environment induced inhibition of corticosterone secretion: physiological evidence for a suprachiasmatic nucleus mediated neuronal hypothalamo-adrenal cortex pathway. Brain Res 758:229–236. https://doi.org/10.1016/S0006-8993(97)00234-5

Buijs RM, Wortel J, Van Heerikhuize JJ, Feenstra MG, Ter Horst GJ, Romijn HJ, Kalsbeek A (1999) Anatomical and functional demonstration of a multisynaptic suprachiasmatic nucleus adrenal (cortex) pathway. Eur J Neurosci 11:1535–1544

Buijs FN, Cazarez F, Basualdo MC, Scheer FAJL, Perusquía M, Centurion D, Buijs RM (2014) The suprachiasmatic nucleus is part of a neural feedback circuit adapting blood pressure response. Neuroscience 266:197–207. https://doi.org/10.1016/j.neuroscience.2014.02.018

Buijs FN, Guzmán-Ruiz M, León-Mercado L, Basualdo MC, Escobar C, Kalsbeek A, Buijs RM (2017) Suprachiasmatic nucleus interaction with the arcuate nucleus; Essential for organizing physiological rhythms. eNeuro 4:1–14. https://doi.org/10.1523/ENEURO.0028-17.2017

Buijs RM, Guzmán Ruiz MA, Méndez Hernández R, Rodríguez Cortés B (2019) The suprachiasmatic nucleus; a responsive clock regulating homeostasis by daily changing the setpoints of physiological parameters. Auton Neurosci Basic Clin 218:43–50. https://doi.org/10.1016/j.autneu.2019.02.001

Cahill DJ, Wardle PG, Harlow CR, Hull MG (1998) Onset of the preovulatory luteinizing hormone surge: diurnal timing and critical follicular prerequisites. Fertil Steril 70:56–59. https://doi.org/10.1016/s0015-0282(98)00113-7

Dietrich MO, Zimmer MR, Bober J, Horvath TL (2015) Hypothalamic Agrp neurons drive stereotypic behaviors beyond feeding. Cell 160:1222–1232

Engeland WC, Arnhold MM (2005) Neural circuitry in the regulation of adrenal corticosterone rhythmicity. Endocrine 28:325–332. https://doi.org/10.1385/ENDO:28:3:325

Estrada KM, Clay CM, Pompolo S, Smith JT, Clarke IJ (2006) Elevated KiSS-1 expression in the arcuate nucleus prior to the cyclic preovulatory gonadotrophin-releasing hormone/lutenising hormone surge in the ewe suggests a stimulatory role for kisspeptin in oestrogen-positive feedback. J Neuroendocrinol 18:806–809. https://doi.org/10.1111/j.1365-2826.2006.01485.x

Everett JW, Sawyer CH (1950) A 24-hour periodicity in the "LH-release apparatus" of female rats, disclosed by barbiturate sedation. Endocrinology 71:198–218. https://doi.org/10.1210/endo-47-3-198

Freeman GM, Herzog ED (2011) Neuropeptides go the distance for circadian synchrony. Proc Natl Acad Sci U S A 108:13883–13884. https://doi.org/10.1073/pnas.1110844108

Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB (2005) Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 28:1289–1296

Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D (2006) Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension 47:833–839. https://doi.org/10.1161/01.HYP.0000217362.34748.e0

Gerendai I, Toth IE, Boldogkoi Z, Medveczky I, Halasz B (2000) CNS structures presumably involved in vagal control of ovarian function. J Auton Nerv Syst 80:40–45

Gizowski C, Bourque CW (2020) Sodium regulates clock time and output via an excitatory GABAergic pathway. Nature 583:421–424. https://doi.org/10.1038/s41586-020-2471-x

Gizowski C, Zaelzer C, Bourque CW (2016) Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep. Nature 537:685–688

Goncharuk VD, Van Heerikhuize J, Dai JP, Swaab DF, Buijs RM (2001) Neuropeptide changes in the suprachiasmatic nucleus in primary hypertension indicate functional impairment of the

biological clock. J Comp Neurol 431:320–330. https://doi.org/10.1002/1096-9861(20010312)431:3<320::AID-CNE1073>3.0.CO;2-2

Gropp E, Shanabrough M, Borok E, Xu AW, Janoschek R, Buch T, Plum L, Balthasar N, Hampel B, Waisman A, Barsh GS, Horvath TL, Brüning JC (2005) Agouti-related peptide-expressing neurons are mandatory for feeding. Nat Neurosci 8:1289–1291. https://doi.org/10.1038/nn1548

Guzmán-Ruiz M, Saderi N, Cazarez-Márquez F, Guerrero-Vargas NN, Basualdo MC, Acosta-Galván G, Buijs RM (2014) The suprachiasmatic nucleus changes the daily activity of the arcuate nucleus α-MSH neurons in male rats. Endocrinology 155:525–535. https://doi.org/10.1210/en.2013-1604

Guzmán-Ruiz MA, Ramirez-Corona A, Guerrero-Vargas NN, Sabath E, Ramirez-Plascencia OD, Fuentes-Romero R, León-Mercado LA, Sigales MB, Escobar C, Buijs RM (2015) Role of the suprachiasmatic and arcuate nuclei in diurnal temperature regulation in the rat. J Neurosci 35:15419–15429. https://doi.org/10.1523/JNEUROSCI.1449-15.2015

Hogenboom R, Kalsbeek MJ, Korpel NL, de Goede P, Koenen M, Buijs RM, Romijn JA, Swaab DF, Kalsbeek A, Yi C-X (2019) Loss of arginine vasopressin- and vasoactive intestinal polypeptide-containing neurons and glial cells in the suprachiasmatic nucleus of individuals with type 2 diabetes. Diabetologia 62:2088–2093. https://doi.org/10.1007/s00125-019-4953-7

Ishida A, Mutoh T, Ueyama T, Bando H, Masubuchi S, Nakahara D, Tsujimoto G, Okamura H (2005) Light activates the adrenal gland: timing of gene expression and glucocorticoid release. Cell Metab 2:297–307. https://doi.org/10.1016/j.cmet.2005.09.009

Jones JR, Simon T, Lones L, Herzog ED (2018) SCN VIP neurons are essential for normal light-mediated resetting of the circadian system. J Neurosci 38:7986–7995

Kalsbeek A, Van Heerikhuize JJ, Wortel J, Buijs RM (1996) A diurnal rhythm of stimulatory input to the hypothalamo-pituitary-adrenal system as revealed by timed intrahypothalamic administration of the vasopressin V1 antagonist. J Neurosci 16:5555–5565

Kalsbeek A, Ruiter M, La Fleur SE, Van Heijningen C, Buijs RM (2003) The diurnal modulation of hormonal responses in the rat varies with different stimuli. J Neuroendocrinol 15:1144–1155

Karssen AM, Meijer OC, van der Sandt IC, Lucassen PJ, de Lange EC, de Boer AG, de Kloet ER (2001) Multidrug resistance P-glycoprotein hampers the access of cortisol but not of corticosterone to mouse and human brain. Endocrinology 142:2686–2694

Kerdelhue B, Brown S, Lenoir V, Queenan JT Jr, Jones GS, Scholler R, Jones HW Jr (2002) Timing of initiation of the preovulatory luteinizing hormone surge and its relationship with the circadian cortisol rhythm in the human. Neuroendocrinology 75:158–163

Klingman KM, Marsh EE, Klerman EB, Anderson EJ, Hall JE (2011) Absence of circadian rhythms of gonadotropin secretion in women. J Clin Endocrinol Metab 96:1456–1461. https://doi.org/10.1210/jc.2010-2739

Kreier F, Fliers E, Voshol PJ, Van Eden CG, Havekes LM, Kalsbeek A, Van Heijningen CL, Sluiter AA, Mettenleiter TC, Romijn JA, Sauerwein HP, Buijs RM (2002) Selective parasympathetic innervation of subcutaneous and intra-abdominal fat—functional implications. J Clin Invest 110:1243–1250. https://doi.org/10.1172/JCI0215736

Kreier F, Yilmaz A, Kalsbeek A, Romijn JA, Sauerwein HP, Fliers E, Buijs RM (2003) Hypothesis: shifting the equilibrium from activity to food leads to autonomic unbalance and the metabolic syndrome. Diabetes. https://doi.org/10.2337/diabetes.52.11.2652

Kreier F, Kap YS, Mettenleiter TC, Van Heijningen C, Van Der Vliet J, Kalsbeek A, Sauerwein HP, Fliers E, Romijn JA, Buijs RM (2006) Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. Endocrinology 147:1140–1147. https://doi.org/10.1210/en.2005-0667

Langlet F, Levin BE, Luquet S, Mazzone M, Messina A, Dunn-Meynell AA, Balland E, Lacombe A, Mazur D, Carmeliet P, Bouret SG, Prevot V, Dehouck B (2013) Tanycytic VEGF-A boosts blood-hypothalamus barrier plasticity and access of metabolic signals to the arcuate nucleus in response to fasting. Cell Metab 17:607–617

Larsen PJ, Tang-Christensen M, Jessop DS (1997) Central administration of glucagon-like peptide-1 activates hypothalamic neuroendocrine neurons in the rat. Endocrinology 138:4445–4455

Legan SJ, Karsch FJ (1975) A daily signal for the LH surge in the rat. Endocrinology 96:57–62. https://doi.org/10.1210/endo-96-1-57

Leon-Mercado L, Chao DHM, Basualdo MC, Kawata M, Escobar C, Buijs RM (2017) The arcuate nucleus: a site of fast negative feedback for corticosterone secretion in male rats. eNeuro 4:1–14. https://doi.org/10.1523/ENEURO.0350-16.2017

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RSE, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223. https://doi.org/10.1056/NEJMoa051688

Liu S, Chen XM, Yoda T, Nagashima K, Fukuda Y, Kanosue K (2002) Involvement of the suprachiasmatic nucleus in body temperature modulation by food deprivation in rats. Brain Res 929:26–36

Matsuyama S, Ohkura S, Mogi K, Wakabayashi Y, Mori Y, Tsukamura H, Maeda KI, Ichikawa M, Okamura H (2011) Morphological evidence for direct interaction between kisspeptin and gonadotropin-releasing hormone neurons at the median eminence of the male goat: an immunoelectron microscopic study. Neuroendocrinology 94:323–332. https://doi.org/10.1159/000331576

Mazuski C, Chen SP, Herzog ED (2020) Different roles for VIP neurons in the neonatal and adult suprachiasmatic nucleus. J Biol Rhythms 35:465–475. https://doi.org/10.1177/0748730420932073

Mimee A, Smith PM, Ferguson AV (2013) Circumventricular organs: targets for integration of circulating fluid and energy balance signals? Physiol Behav. https://doi.org/10.1016/j.physbeh.2013.02.012

Mirmiran M, Swaab DF, Witting W, Honnebier MBOM, Van Gool WA, Eikelenboom P (1989) Biological clocks in development, aging and Alzheimer's disease. Brain Dysfunct 2:57–66

Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, Lai J, Ciofi P, McMullen NT, Rance NE (2012a) Arcuate kisspeptin/neurokinin B/dynorphin (KNDy) neurons mediate the estrogen suppression of gonadotropin secretion and body weight. Endocrinology 153:2800–2812

Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, McMullen NT, Rance NE (2012b) Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. Proc Natl Acad Sci USA 109:19846–19851

Modabbernia A, Heidari P, Soleimani R, Sobhani A, Roshan ZA, Taslimi S, Ashrafi M, Modabbernia MJ (2014) Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. J Psychiatr Res 53:133–140. https://doi.org/10.1016/j.jpsychires.2014.02.013

Mostafavi A, Solhi M, Mohammadi M-R, Hamedi M, Keshavarzi M, Akhondzadeh S (2014) Melatonin decreases olanzapine induced metabolic side-effects in adolescents with bipolar disorder: a randomized double-blind placebo-controlled trial. Acta Med Iran 52:734–739

Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD (2018) A neural circuit underlying the generation of hot flushes. Cell Rep 24:271–277. https://doi.org/10.1016/j.celrep.2018.06.037

Padilla SL, Perez JG, Ben-Hamo M, Johnson CW, Sanchez REA, Bussi IL, Palmiter RD, de la Iglesia HO (2019) Kisspeptin neurons in the arcuate nucleus of the hypothalamus orchestrate circadian rhythms and metabolism. Curr Biol 29:592–604.e4. https://doi.org/10.1016/j.cub.2019.01.022

Palm IF, Van Der Beek EM, Wiegant VM, Buijs RM, Kalsbeek A (1999) Vasopressin induces a luteinizing hormone surge in ovariectomized, estradiol-treated rats with lesions of the suprachiasmatic nucleus. Neuroscience 93:659–666. https://doi.org/10.1016/S0306-4522(99)00106-2

Palm IF, Van Der Beek EM, Wiegant VM, Buijs RM, Kalsbeek A (2001) The stimulatory effect of vasopressin on the luteinizing hormone surge in ovariectomized, estradiol-treated rats is time-dependent. Brain Res 901:109–116

Perreau-Lenz S, Kalsbeek A, Pévet P, Buijs RM (2004) Glutamatergic clock output stimulates melatonin synthesis at night. Eur J Neurosci 19:318–324. https://doi.org/10.1111/j.0953-816X.2003.03132.x

Perreau-Lenz S, Kalsbeek A, Van Der Vliet J, Pévet P, Buijs RM (2005) In vivo evidence for a controlled offset of melatonin synthesis at dawn by the suprachiasmatic nucleus in the rat. Neuroscience 130:797–803. https://doi.org/10.1016/j.neuroscience.2004.10.014

Ramírez DA, Vieyra E, González AI, Morán C, Domínguez R, Morales-Ledesma L (2017) Both the suprachiasmatic nucleus and the superior ovarian nerve contribute to the processes of ovulation and steroid hormone secretion on proestrus. Reprod Sci 24:844–855. https://doi.org/10.1177/1933719116670307

Rometo AM, Krajewski SJ, Voytko ML, Rance NE (2007) Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys. J Clin Endocrinol Metab 92(7):2744–2750

Romo-Nava F, Alvarez-Icaza González D, Fresán-Orellana A, Saracco Alvarez R, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G, Buijs RM (2014) Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord 16:410–421. https://doi.org/10.1111/bdi.12196

Romo-Nava F, Buijs FN, Valdés-Tovar M, Benítez-King G, Basualdo MC, Perusquía M, Heinze G, Escobar C, Buijs RM (2017) Olanzapine-induced early cardiovascular effects are mediated by the biological clock and prevented by melatonin. J Pineal Res 62:1–14. https://doi.org/10.1111/jpi.12402

Russo KA, La JL, Stephens SB, Poling MC, Padgaonkar NA, Jennings KJ, Piekarski DJ, Kauffman AS, Kriegsfeld LJ (2015) Circadian control of the female reproductive axis through gated responsiveness of the RFRP-3 system to VIP signaling. Endocrinology 156(7):2608–2618

Russo KA, La JL, Stephens SBZ, Poling MC, Padgaonkar NA, Jennings KJ, Piekarski DJ, Kauffman AS, Kriegsfeld LJ (2018) Circadian control of the female reproductive axis to VIP signaling. Endocrinology 156:2608–2618. https://doi.org/10.1210/en.2014-1762

Scarinci E, Tropea A, Notaristefano G, Arena V, Alesiani O, Fabozzi SM, Lanzone A, Apa R (2019) "Hormone of darkness" and human reproductive process: direct regulatory role of melatonin in human corpus luteum. J Endocrinol Invest 42:1191–1197. https://doi.org/10.1007/s40618-019-01036-3

Schwartz WJ, Reppert SM (1985) Neural regulation of the circadian vasopressin rhythm in cerebrospinal fluid: a pre-eminent role for the suprachiasmatic nuclei. J Neurosci 5:2771–2778

Silva C-C, Cortés GD, Javier CY, Flores A, Domínguez R (2020) A neural circadian signal essential for ovulation is generated in the suprachiasmatic nucleus during each stage of the oestrous cycle. Exp Physiol 105:258–269. https://doi.org/10.1113/EP087942

Smith JT, Popa SM, Clifton DK, Hoffman GE, Steiner RA (2006) Kiss1 neurons in the forebrain as central processors for generating the preovulatory luteinizing hormone surge. J Neurosci 26:6687–6694

Swaab DF (2004) Neuropeptides in hypothalamic neuronal disorders. Int Rev Cytol 240:305–375

Teclemariam Mesbah R, Ter Horst GJ, Postema F, Wortel J, Buijs RM (1999) Anatomical demonstration of the suprachiasmatic nucleus- pineal pathway. J Comp Neurol 406:171–182

Togo T, Kojima K, Shoji M, Kase A, Uchikado H, Katsuse O, Iseki E, Kosaka K (2004) Serum adiponectin concentrations during treatment with olanzapine or risperidone: a pilot study. Int Clin Psychopharmacol 19:37–40. https://doi.org/10.1097/00004850-200401000-00007

Uchida K, Okamoto N, Ohara K, Morita Y (1996) Daily rhythm of serum melatonin in patients with dementia of the degenerate type. Brain Res 717:154–159

Van Der Beek EM, Van Oudheusden HJC, Buijs RM, Den Hurk HAV, Den H, Van R, Wiegant VM (1994) Preferential induction of c-fos immunoreactivity in vasoactive intestinal polypeptide-innervated gonadotropin-releasing hormone neurons during a steroid-induced luteinizing

hormone surge in the female rat. Endocrinology 134:2636–2644. https://doi.org/10.1210/endo.134.6.8194489

Van Der Beek EM, Horvath TL, Wiegant VM, Van Den Hurk R, Buijs RM (1997) Evidence for a direct neuronal pathway from the suprachiasmatic nucleus to the gonadotropin-releasing hormone system: combined tracing and light and electron microscopic immunocytochemical studies. J Comp Neurol 384:569–579

Van Der Beek EM, Swarts HJ, Wiegant VM (1999) Central administration of antiserum to vasoactive intestinal peptide delays and reduces luteinizing hormone and prolactin surges in ovariectomized, estrogen-treated rats. Neuroendocrinology 69:227–237. https://doi.org/10.1159/000054423

Vida B, Deli L, Hrabovszky E, Kalamatianos T, Caraty A, Coen CW, Liposits Z, Kallo I (2010) Evidence for suprachiasmatic vasopressin neurones innervating kisspeptin neurones in the rostral periventricular area of the mouse brain: regulation by oestrogen. J Neuroendocrinol 22:1032–1039

Xiao L, Zhang C, Li X, Gong S, Hu R, Balasubramanian R, Crowley W Jr WF, Hastings MH, Zhou Q-Y (2014) Signaling role of prokineticin 2 on the estrous cycle of female mice. PLoS One 9:e90860. https://doi.org/10.1371/journal.pone.0090860

Yi C-X, Van Der Vliet J, Dai J, Yin G, Ru L, Buijs RM (2006) Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. Endocrinology 147:283–294. https://doi.org/10.1210/en.2005-1051

Yilmaz A, Kalsbeek A, Buijs RM (2018) Functional changes of the SCN in spontaneous hypertension but not after the induction of hypertension. Chronobiol Int 1–15. https://doi.org/10.1080/07420528.2018.1469035

Yilmaz A, Buijs FN, Kalsbeek A, Buijs RM (2019) Neuropeptide changes in the suprachiasmatic nucleus are associated with the development of hypertension. Chronobiol Int 36:1072–1087. https://doi.org/10.1080/07420528.2019.1613424

Yip SH, Campos P, Liu X, Porteous R, Herbison AE (2021) Innervation of GnRH neuron distal projections and activation by kisspeptin in a new GnRH-Cre rat model. Endocrinology 162. https://doi.org/10.1210/endocr/bqaa186

Zeman M, Dulková K, Bada V, Herichová I (2005) Plasma melatonin concentrations in hypertensive patients with the dipping and non-dipping blood pressure profile. Life Sci 76:1795–1803. https://doi.org/10.1016/j.lfs.2004.08.034