Daily Regulation of Hormone Profiles

Andries Kalsbeek and Eric Fliers

Abstract The highly coordinated output of the hypothalamic biological clock does not only govern the daily rhythm in sleep/wake (or feeding/fasting) behaviour but also has direct control over many aspects of hormone release. In fact, a significant proportion of our current understanding of the circadian clock has its roots in the study of the intimate connections between the hypothalamic clock and multiple endocrine axes. This chapter will focus on the anatomical connections used by the mammalian biological clock to enforce its endogenous rhythmicity on the rest of the body, using a number of different hormone systems as a representative example. Experimental studies have revealed a highly specialised organisation of the connections between the mammalian circadian clock neurons and neuroendocrine as well as pre-autonomic neurons in the hypothalamus. These complex connections ensure a logical coordination between behavioural, endocrine and metabolic functions that will help the organism adjust to the time of day most efficiently. For example, activation of the orexin system by the hypothalamic biological clock at the start of the active phase not only ensures that we wake up on time but also that our glucose metabolism and cardiovascular system are prepared for this increased activity. Nevertheless, it is very likely that the circadian clock present *within* the endocrine glands plays a significant role as well, for instance, by altering these glands' sensitivity to specific stimuli throughout the day. In this way the net result of the activity of the hypothalamic and peripheral clocks ensures an optimal

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endocrine adaptation of the metabolism of the organism to its time-structured environment.

Keywords Hypothalamus • Autonomic nervous system • Orexin • Glucose • Melatonin • GABA • Liver • TSH

Abbreviations

ACTH	Adrenocorticotrophic hormone
ANS	Autonomic nervous system
AVP	Arginine vasopressin
AVPV	Anteroventral periventricular nucleus
BAT	Brown adipose tissue
CLOCK	Circadian locomotor output cycles kaput
CNS	Central nervous system
CRH	Corticotrophin-releasing hormone
CSF	Cerebrospinal fluid
D2	Type 2 deiodinase
DMH	Dorsomedial nucleus of the hypothalamus
E	Oestrogen
ER	Oestrogen receptor
FFA	Free fatty acid
GABA	Gamma-aminobutyric acid
GnIH	Gonadotropin-inhibitory hormone
GnRH	Gonadotropin-releasing hormone
HPA	Hypothalamo–pituitary–adrenal
HPG	Hypothalamo–pituitary–gonadal
HPT	Hypothalamo–pituitary–thyroid
HSL	Hormone-sensitive lipase
ICU	Intensive care unit
ICV	Intracerebroventricular
IML	Intermediolateral column
L/D	Light/dark
L/L	Light/light, i.e. constant light
LH	Luteinising hormone
LM	Light microscopy
LPL	Lipoprotein lipase
MPOA	Medial preoptic area
NAMPT	Nicotinamide phosphoribosyltransferase
NPFF	Neuropeptide FF
NPY	Neuropeptide Y
OVX	Ovariectomy
PACAP	Pituitary adenylate cyclase-activating polypeptide

PBEF	Pre-B-cell colony-enhancing factor
PeN	Periventricular nucleus
pePVN	Periventricular PVN
Per	Period
PF	Perifornical area
PRV	Pseudo rabies virus
PVN	Paraventricular nucleus of the hypothalamus
Ra	Rate of appearance
RFRP	RF-amide-related peptide
RHT	Retinohypothalamic tract
SCG	Superior cervical ganglion
SCN	Suprachiasmatic nucleus
SEM	Standard error of the mean
SON	Supraoptic nucleus
subPVN	Subparaventricular PVN
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TH	Tyrosine hydroxylase
TRH	Thyrotrophin-releasing hormone
TSH	Thyroid-stimulating hormone
TTX	Tetrodotoxin
VIP	Vasoactive intestinal polypeptide
VMH	Ventromedial nucleus of the hypothalamus
VP	Vasopressin
WAT	White adipose tissue
ZT	Zeitgeber time

1 Introduction

The regular 24-h rotation of the earth has led to the evolution of autonomous circadian clocks in virtually all life forms, from prokaryotes to eukaryotes (Buhr and Takahashi 2013). In mammals, including the humans, the master endogenous clock is located in the brain. In the premodern world, the temporal cycles of feeding and fasting of our ancestors matched the patterns of wakefulness and sleep that corresponded with the daily periods of light and darkness. The circadian clock mechanism in the brain served to coordinate and anticipate our behaviour and metabolism according to this environmental periodicity induced by the earth's rotation. A proper entrainment of the endogenous clock mechanism to the outside world was ensured by a number of input signals, of which light, food intake and locomotor activity are still the most important ones.

The circadian or biological clock, located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, consists of several clusters of small and densely packed neurons in which various peptidergic transmitters are expressed (Moore 1996a). The entraining signals from light, feeding and locomotor activity are relayed to the SCN via direct projections from the retina, the hypothalamic arcuate nucleus and the raphe nucleus, respectively. The direct projection from the intergeniculate leaflet to the SCN seems to be an important secondary route for all three entraining signals. The afferent projections from these different brain structures use various neurotransmitters, including glutamate, PACAP, neuropeptide Y (NPY), neuropeptide FF (NPFF) and serotonin (Challet and Pévet 2003). The endogenous clock mechanism consists of interlocking transcriptional–translational feedback loops and contains genes necessary for oscillator maintenance ('core clock genes'), as well as specific clock-controlled output genes that impose their rhythmicity on the rest of the hypothalamus and beyond (Buhr and Takahashi 2013; Takahashi et al. 2008). A few of the peptidergic SCN transmitters, i.e. vasopressin (VP), vasoactive intestinal peptide (VIP), cardiotrophin-like cytokine and prokineticin-2, have already been identified as so-called clock-controlled genes (Hahm and Eiden 1998; Jin et al. 1999; Cheng et al. 2002; Kraves and Weitz 2006). Subsequently, the rhythmic output of this endogenous clock is conveyed to, among other things, endocrine systems. In this chapter we will show how the SCN uses its efferent projections to different combinations of intermediate, neuroendocrine and pre-autonomic neurons in the hypothalamus to translate its circadian activity into the rhythmic release of glucocorticoids, luteinising hormone (LH), melatonin, insulin, glucagon and leptin (Buijs and Kalsbeek 2001).

2 SCN Outputs

In 1972, it became clear that the SCN in the anterior hypothalamus is the seat of the central biological clock (Weaver 1998). Only a few years after this discovery, it was demonstrated that the SCN contains a prominent population of VP-containing neurons (Vandesande et al. 1974; Swaab et al. 1975). Due to its pronounced day/night rhythm in the cat cerebral spinal fluid (CSF) (Reppert et al. 1981, 1987), VP was soon identified as an output of the SCN. This important finding was followed by reports on VP-containing neurons in the SCN of a large variety of species, including man (Sofroniew and Weindl 1980; Stopa et al. 1984; Swaab et al. 1985; Cassone et al. 1988; Reuss et al. 1989; Goel et al. 1999; Smale and Boverhof 1999), as well as CSF VP rhythms in a number of species, including monkey, rat, guinea pig, goat, sheep and rabbit (Günther et al. 1984; Seckl and Lightman 1987; Stark and Daniel 1989; Forsling 1993; Robinson and Coombes 1993). Lesions of the paraventricular nucleus of the hypothalamus (PVN), hypophysectomy and pinealectomy were unable to eliminate this rhythm. The rhythms were even sustained

after complete isolation—by circular knife cuts—of the SCN in vivo. Only complete SCN lesions abolished the rhythm and in most cases reduced the amount of CSF VP to below detection level (Schwartz and Reppert 1985; Jolkonen et al. 1988). In addition, it was demonstrated that also in vitro the rhythmic release of VP from the SCN is maintained for several days (Earnest and Sladek 1986; Gillette and Reppert 1987). Additional studies showed an elevation, or poly-A tail elongation, of VP mRNA in the SCN during the light period (Uhl and Reppert 1986; Robinson et al. 1988). VP mRNA in the PVN and supraoptic nucleus (SON), on the other hand, showed no such diurnal fluctuations. Similar observations, i.e. pronounced daily fluctuations in the SCN, but not in the PVN and SON, were made for the extracellular concentrations of VP in the SCN, PVN and SON (Kalsbeek et al. 1995). The daily fluctuations of VP in the CSF are a result of the day/night rhythm in the firing rate of VP-containing SCN neurons (Buijs et al. 2006) and of the close proximity of the VP-containing SCN projections to the ventricular space, i.e. in the medial preoptic area (MPOA), the periventricular and subparaventricular nucleus (pePVN and subPVN), the dorsomedial hypothalamus (DMH) and the paraventricular nucleus of the thalamus. Since then, many SCN transmitters other than VP have come to be recognised (Morin et al. 2006), many of which also show a clear day/night rhythm in the amount of protein or mRNA expression in the nucleus itself. In the meantime, besides VP, also VIP has been demonstrated to be secreted in a circadian rhythm in vivo (Francl et al. 2010). Despite the clear demonstration with transplantation experiments that humoral factors suffice for reinstating circadian rhythms in locomotor activity and feeding and drinking behaviour (Drucker-Colin et al. 1984; Ralph et al. 1990; Silver et al. 1996), transplantation and parabiosis experiments have also unequivocally demonstrated that non-neuronal mechanisms do not suffice when it comes to reinstating circadian rhythms in all peripheral organs (Lehman et al. 1987; Meyer-Bernstein et al. 1999; Guo et al. 2005). Moreover, an elegant experiment by de la Iglesia et al. (2003) provided clear functional evidence for the necessity of point-to-point neural connections if neuroendocrine rhythms were to be sustained.

So where does the rhythmic information generated within the SCN go? Information on the distribution of SCN projections was initially obtained from neuroanatomical studies using tracing, immunocytochemistry, SCN lesions or a combination of these methods (Hoorneman and Buijs 1982; Watts and Swanson 1987; Kalsbeek et al. 1993a). All these studies showed that the outflow of SCN information was in fact surprisingly limited and pertained to the medial hypothalamus, in particular to target areas that contain mainly interneurons, such as the MPOA, DMH and the subPVN. Direct connections to neuroendocrine neurons (i.e. corticotrophin-releasing hormone (CRH)-, thyrotrophin-releasing hormone (TRH)-, tyrosine hydroxylase (TH)- and gonadotropin-releasing hormone (GnRH)-containing) in the PVN, arcuate nucleus and MPOA, and pre-autonomic neurons in the PVN were more scarce, but were reported as well (Vrang et al. 1995, 1997; Hermes et al. 1996; Teclemariam-Mesbah et al. 1997; Kalsbeek et al. 2000b; De La Iglesia et al. 1995; Van Der Beek et al. 1993, 1997). In the following

paragraphs we will explain how the SCN uses these neural connections to control peripheral rhythms in hormone release (Buijs and Kalsbeek 2001; Kalsbeek and Buijs 2002; Kalsbeek et al. 2006).

3 The Daily Cortisol/Corticosterone Rhythm

The medial parvocellular part of the PVN contains neuroendocrine neurons that synthesise CRH. Together they represent the major determinant of the set point of the neuroendocrine pathway known as the hypothalamo–pituitary–adrenal (HPA) axis (Watts 2005). In about half of the neuroendocrine CRH neurons, VP is co-expressed, with their axons projecting to the median eminence and releasing CRH and VP into the portal circulation to stimulate the adrenocorticotrophic hormone (ACTH)-producing cells in the anterior pituitary. ACTH, in its turn, controls the release of corticosterone through its stimulatory action on the adrenal cortex via the melanocortin receptor type 2. In the neuroanatomical tracing studies mentioned above, the PVN showed up as an important target area of the SCN. The close proximity of (VP-containing) SCN nerve endings near CRH-containing neurons in the PVN gave rise to the hypothesis that, via this projection, circadian information would be imprinted onto the HPA axis. In view of all the evidence in favour of an important role for VP in the output from the SCN, we began, in 1992, with microinfusions of VP and one of its antagonists. These first experiments demonstrated that VP released from SCN terminals has a strong inhibitory control over basal plasma corticosterone concentrations (Kalsbeek et al. 1992). Further studies on the relation between the circadian release of VP and the control of the daily rhythm in the activity of the hypothalamo–pituitary–adrenal (HPA) axis revealed that VP release in the rat DMH is important for ensuring low circulating levels of corticosterone during the first half of the light period (Kalsbeek et al. 1996c). In addition, the subsequent halt of VP release from these SCN terminals in the DMH is a prerequisite for the daily surge in plasma corticosterone before the onset of the main activity period of the nocturnal rat, i.e. the dark period (Kalsbeek et al. 1996b). The important role of VP in the propagation of output signals of the SCN into the PVN was nicely confirmed in a series of experiments using multielectrode recordings in hypothalamic brain slices (Tousson and Meissl 2004). These experiments showed that the circadian rhythm in spontaneous firing rate of PVN neurons was lost in slices from which the SCN had been surgically removed, but could be reinstated by either cocultures of SCN tissue or a rhythmic (12-h on, 12-h off) perfusion of VP. Moreover, simultaneous perfusion with a VP antagonist abolished PVN rhythms during coculture and rhythmic VP perfusion experiments, but not in intact slices. Together, these series of experiments clearly showed that VP is an important, but not the sole, SCN signal involved in the control of the daily rhythm in HPA-axis activity. Moreover, they formed the basis for the novel concept of SCN control over daily hormone rhythms as a push-and-pull or ying–yang mechanism, based upon alternating stimulatory and inhibitory inputs to the

appropriate target neurons. Several experiments in the years following have made a strong case for VIP as a second SCN transmitter involved in the control of the daily corticosterone rhythm (Alexander and Sander 1994; Loh et al. 2008), but its precise role is as yet unclear. Neuromedin U, too, has been proposed to be a stimulatory SCN signal (Graham et al. 2005).

In the case of the HPA axis, at first sight, the most likely target neurons appeared to be the CRH-containing neurons in the PVN. However, some evidence was inconsistent with this role for CRH neurons. First, a direct effect of VP on the CRH neuron would imply a clear daily rhythm in plasma ACTH concentrations, but this was not observed. Second, the observed inhibitory effect of VP was not in line with the usual excitatory effect of VP on its target neurons. Third, contrary to the expected abundant contacts between SCN-derived VP fibres and CRH neurons, only a limited number of such connections were found (Vrang et al. 1995; Buijs and Van Eden 2000). A detailed anatomical scheme incorporating all of the above and explaining our current view on the SCN control of the daily rhythm in HPA activity is shown in Fig. 1. The proposed intermediate role of the gamma-aminobutyric acid (GABA) ergic neurons in the subPVN and DMH in rats is supported by electrophysiological in vitro experiments using hypothalamic slices (Hermes et al. 2000). As the right-hand side image in Fig. 1 shows, the proposed important role for intermediate areas such as the subPVN and DMH also provides a good explanation for the mechanism behind the 12-h reversal of certain rhythms in nocturnal and diurnal species (for instance, that of HPA-axis activity) (Kalsbeek et al. 2008b), when the phase of SCN activity (including VP release) appears to be similar for nocturnal and diurnal species (Cuesta et al. 2009; Dardente et al. 2004).

An important spin-off of the above-mentioned VP experiments was the insight it provided into the outflow of SCN information to the autonomic nervous system (ANS) as an important mediator for the SCN control of peripheral organs and tissues. The mismatch between plasma ACTH and plasma corticosterone concentrations and responses made us realise that the ANS might be important for regulating the sensitivity of the adrenal cortex to ACTH. Transneuronal virus tracing from the adrenal did indeed reveal second-order labelling in PVN neurons and third-order labelling in SCN neurons (Buijs et al. 1999). The functional importance of this multi-synaptic neural connection between the SCN and the adrenal cortex for the daily rhythm in adrenal corticosterone release was proven later on by a series of adrenal microdialysis, adrenal denervation and adrenal transplantation studies (Jasper and Engeland 1994; Ishida et al. 2005; Oster et al. 2006). Recently, Horacio de la Iglesia and coworkers provided an additional piece of evidence for the two-stage control of the circadian corticosterone rhythm using their elegant splitting model. In hamsters, exposure to constant light (LL) conditions can induce ‘splitting’, which results in the circadian day doubling in frequency. In split animals, rest activity, body temperature and hormone secretion rhythms peak twice per day instead of once (Pittendrigh and Daan 1976; Pickard et al. 1984; Swann and Turek 1985). As expected, the unsplit hamsters showed a single peak of cortisol release concomitant with a single peak of ACTH release. Split hamsters, on the other hand, showed two peaks of plasma cortisol that

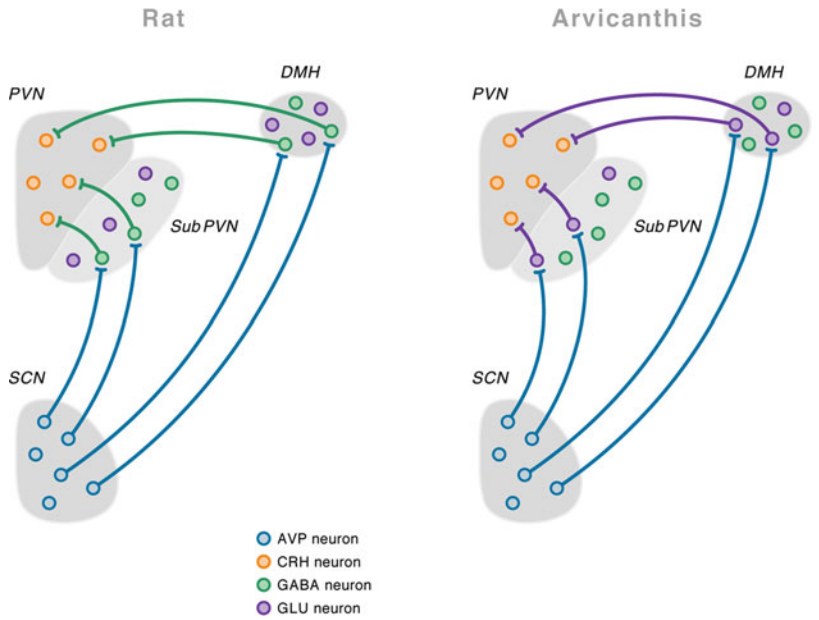

Fig. 1 Detailed anatomical scheme of demonstrated and putative connections of the suprachiasmatic nucleus (SCN) in the nocturnal rat and the diurnal *Arvicanthis ansorgei* brain to explain the opposite effects of arginine vasopressin (AVP) on the hypothalamic–pituitary–adrenal axis in these two species. AVP is released during the light period, both in the nocturnal rat and the diurnal *A. ansorgei*. In rats, AVP release during the light period will inhibit the corticotropin-releasing hormone (CRH)-containing neurons in the paraventricular nucleus of the hypothalamus (PVN) by contacting gamma-aminobutyric acid (GABA)ergic interneurons in the subPVN and dorsomedial nucleus of the hypothalamus (DMH). On the other hand, in the *A. ansorgei*, AVP release during the light period will stimulate CRH-containing neurons because it acts on the glutamatergic (GLU), instead of GABAergic, interneurons in the subPVN and DMH

were ~12 h apart but, surprisingly, did not rely on the rhythmic release of ACTH (Lilley et al. 2012). The SCN thus apparently uses a two-stage mechanism to control daily hormone rhythms: on the one hand it acts on the neuroendocrine motor neurons to influence the release of hypothalamic releasing factors, and on the other hand it also acts—through the ANS—on the target tissues to influence the sensitivity to the incoming hormonal message.

4 The Daily Melatonin Rhythm

The prime example of circadian control through the autonomic nervous system is the daily rhythm in melatonin release from the pineal gland. As early as the early 1940s, Bargman (1943) suggested that the endocrine function of the pineal gland was regulated by light, via the central nervous system. In the late 1950s, the

hormone synthesised and released by the pineal gland was identified as *N*-acetyl-5-metoxytryptamine and named melatonin by Lerner et al. (1958). The daily rhythm in pineal melatonin content, with low levels during the day and high levels during the night, was among the first hormonal rhythms to be described as a true circadian rhythm (Ralph et al. 1971; Lynch 1971). Shortly after the establishment of the SCN as the seat of the mammalian endogenous clock, a diagram was published that presented a very close approximation of the central nervous pathway controlling the circadian rhythm of pineal melatonin synthesis (Moore and Klein 1974). The pathway was unusual in the sense that it passed through both central and peripheral neural structures, i.e. contrary to the control of the daily corticosterone rhythm, which at that time only seemed to involve neuroendocrine mechanisms. The central pathway was suggested to consist of three components (1) a visual pathway transmitting information concerning environmental light intensity to the endogenous clock, (2) an output pathway of the endogenous clock transmitting its information to the spinal cord, and (3) a sympathetic pathway to the pineal gland originating from preganglionic sympathetic neurons in the intermediolateral column (IML) of the spinal cord. The early work of Kappers (1960) established the details of the peripheral sympathetic innervation of the pineal gland in the rat, whereas its functional importance was shown by Klein et al. (1971). The early works of Moore and Klein (1974) and Klein and Moore (1979) established the importance of the retinohypothalamic tract (RHT). Additional experiments involving extirpation of the superior cervical ganglion (SCG) and transection of the spinal cord established the functional importance of the sympathetic innervation (Wurtman et al. 1967; Klein et al. 1971; Bowers et al. 1984; Moore 1978; Reiter et al. 1982; Axelrod 1974; Kneisley et al. 1978). The daily rhythm in the synthesis and release of melatonin is thus ultimately controlled by the sympathetic input to the pineal gland (Moore 1996b; Drijfhout et al. 1996). A similar pathway, with potential relevance for sleep disturbances, is most likely to be present in humans (Zeitzer et al. 2000; Scheer et al. 2006). However, the details of the central pathway between the SCN and spinal cord remained enigmatic for a long time.

The first SCN lesion studies quickly proved the indispensability of the SCN for the daily rhythmicity of melatonin synthesis (Bittman et al. 1989; Moore and Klein 1974; Tessonneaud et al. 1995). Initially, it was suggested that the SCN/spinal cord pathway would involve the hypothalamic retrochiasmatic area or the lateral hypothalamus, the medial forebrain bundle and the medullary reticular formation (Klein and Moore 1979; Moore and Klein 1974). Then the first histochemical studies identified SCN projections to the PVN (Berk and Finkelstein 1981; Swanson and Cowan 1975; Stephan et al. 1981). In combination with the PVN/spinal cord projections described shortly before (Swanson and Kuypers 1980), this resulted in the identification of the PVN as an important relay for SCN output to the spinal cord (Klein et al. 1983). The key importance of the PVN as a target area for SCN information for the melatonin rhythm was corroborated by a number of subsequent neurotoxin and knife-cut studies (Bittman et al. 1989; Hastings and Herbert 1986; Lehman et al. 1984; Smale et al. 1989; Johnson et al. 1989; Pickard and Turek 1983; Badura et al. 1989; Nunez et al. 1985) and by studies involving electrical

stimulation of the PVN (Reuss et al. 1985; Olcese et al. 1987; Yanovski et al. 1987). However, it was only at the close of the twentieth century that the retrograde trans-synaptic virus tracing technique made it possible to map out the entire pathway (Larsen et al. 1998; Teclemariam-Mesbah et al. 1999). Although the viral tracing studies had helped to clearly define the total neuronal pathway, the respective roles of each of the relay stations in the control of the melatonin synthesis rhythm still remained to be determined. Besides, the different neurotransmitters used in each step of the pathway, as well as their specific daily pattern of release, remained to be brought to light.

VP became the first neurotransmitter proposed to have an inhibitory role in the control of melatonin rhythm, as it is released by the SCN with a phase which is the reverse of that of melatonin release from the pineal gland (i.e. with a peak release during the light period). Nevertheless, the first studies using VP-deficient Brattleboro rats did not reveal any difference in pineal melatonin synthesis except for the phase of the rhythm (Reuss et al. 1990; Schröder et al. 1988a). Although some studies did describe modulatory effects of the SCN transmitters VP and VIP on pineal activity, the experimental setup in these studies did not allow any definitive conclusions about the site of action of these neurotransmitters (Yuwiler 1983; Schröder et al. 1988b, 1989; Stehle et al. 1991; Reuss et al. 1990). In our own experiments, microinfusions of VP or VIP into the PVN during the initial 7 h of the dark period only produced a small stimulatory effect on plasma melatonin levels, but not the expected inhibitory effect (Kalsbeek et al. 1993b). In a later replication study, in which pineal melatonin release was used as a read-out instead of plasma melatonin, again no inhibitory effects of VP could be detected when applied at the level of the PVN (Kalsbeek et al. 2000c). On the other hand, local administration of VP in the pineal did cause a temporary increase of pineal melatonin release (Barassin et al. 2000).

In the meantime, more and more evidence pointed to the potential importance of GABA for SCN function. GABA was shown to be abundantly present in the SCN, even in projecting cells (Buijs et al. 1994; Hermes et al. 1996; Moore and Speh 1993; Okamura et al. 1989; Van Den Pol and Gorcs 1986), and we decided to test the functionality of this GABAergic output. As a first step we were able to mimic the inhibitory effect of nocturnal light exposure by administering the GABA agonist muscimol to the PVN (Kalsbeek et al. 1996a). In a follow-up study, we managed to prevent the inhibitory effect of light on nocturnal melatonin release by infusing the GABA antagonist bicuculline within the PVN, which demonstrated that light-induced inhibition of melatonin synthesis in the rat requires GABA release in the PVN (Kalsbeek et al. 1999). Next, we showed that GABA was also involved in the circadian inhibition of melatonin synthesis, independent of its role in the direct inhibitory effect of light. Indeed, blocking GABAergic transmission in the PVN during (subjective) daytime increases melatonin synthesis (Kalsbeek et al. 2000c). Based on these results and assuming an intrinsic and constant activity of the pre-autonomic PVN neurons, we proposed that the SCN controls the rhythm of melatonin synthesis by imposing an inhibitory GABAergic signal onto the PVN/pineal pathway during (subjective) daytime. However, follow-up studies conducted

in our group revealed that the melatonin rhythm obeys an even more complex power. Indeed, lesion studies comparing the effect of lesioning on melatonin synthesis of either the SCN, the PVN, or the SCG, revealed that the SCG and the PVN are just simple relay stations of SCN outputs to the pineal gland (Perreau-Lenz et al. 2003). The results of this study also proved that the rhythm of melatonin synthesis is not formed by a single circadian (daytime) inhibitory signal to the PVN but by a combination of this inhibitory signal with a stimulatory input to the PVN, also derived from the SCN. Therefore, as proposed in the foregoing for the control of corticosterone by the SCN, the SCN also seems to use multiple outputs for the control of melatonin synthesis. Looking at the mean levels of corticosterone and melatonin in SCN-lesioned animals in comparison with the peak levels in intact animals (Fig. 2), it is clear that the stimulatory part of the SCN output is even more important for the generation of the melatonin rhythm than for the generation of the corticosterone rhythm. However, the main neuronal activity of the SCN during daytime (Bos and Mirmiran 1990; Inouye and Kawamura 1979; Schwartz and Gainer 1977; Shibata et al. 1982) seems to be in clear contradiction with such a pronounced stimulatory role during the dark period. Nevertheless, it was not until 1996 that Moore noticed the apparent contradiction between the nocturnal silence of SCN neurons and the stimulation of melatonin synthesis. We tested this idea of a stimulatory role of the SCN at night in vivo (Perreau-Lenz et al. 2004), by measuring the acute effects of a temporary shutdown of the neuronal activity in the SCN on melatonin release. Nocturnal pineal melatonin release was measured by means of microdialysis before, during and after a local tetrodotoxin (TTX) application of 2 h by reverse dialysis within the SCN. This intervention resulted in an immediate diminution of melatonin secretion and an increased release of corticosterone, which shows that a generally weak neuronal activity of the SCN at night still has important physiological implications. The SCN nocturnal neuronal activity is sufficient and, more importantly, necessary to stimulate melatonin synthesis and to inhibit corticosterone at the same time. Interestingly, unlike the blockade of GABAergic transmission within the PVN (Kalsbeek et al. 2000c), TTX infusion within the SCN during daytime did not induce any increase of melatonin levels. Apparently, silencing the total neuronal activity of the SCN during daytime does not have the same effect on melatonin synthesis as does selective blocking of the SCN inhibitory transmission to the PVN. Consequently, we propose that the SCN also sustains a stimulatory output to the PVN during daytime, the final effect of which, in normal conditions, is overwhelmed by the simultaneous activity of the inhibitory GABAergic output to the PVN. Indeed, the existence of 16 % of non-rhythmic cells in the SCN (Nakamura et al. 2001) supports the idea of a tonic SCN stimulatory output originating from the same cells throughout the 24-h period. In addition, other studies showing that not all SCN neurons have the same phase of neuronal activity (Herzog et al. 1997; Nakamura et al. 2001; Saeb-Parsy and Dyball 2003; Schaap et al. 2003) suggest that the SCN could even sustain several stimulatory outputs—originating from different cell groups—at different time points.

Our ideas on the combined inhibitory and stimulatory outputs of the SCN are in agreement with studies indicating that both GABA and glutamate may be used as

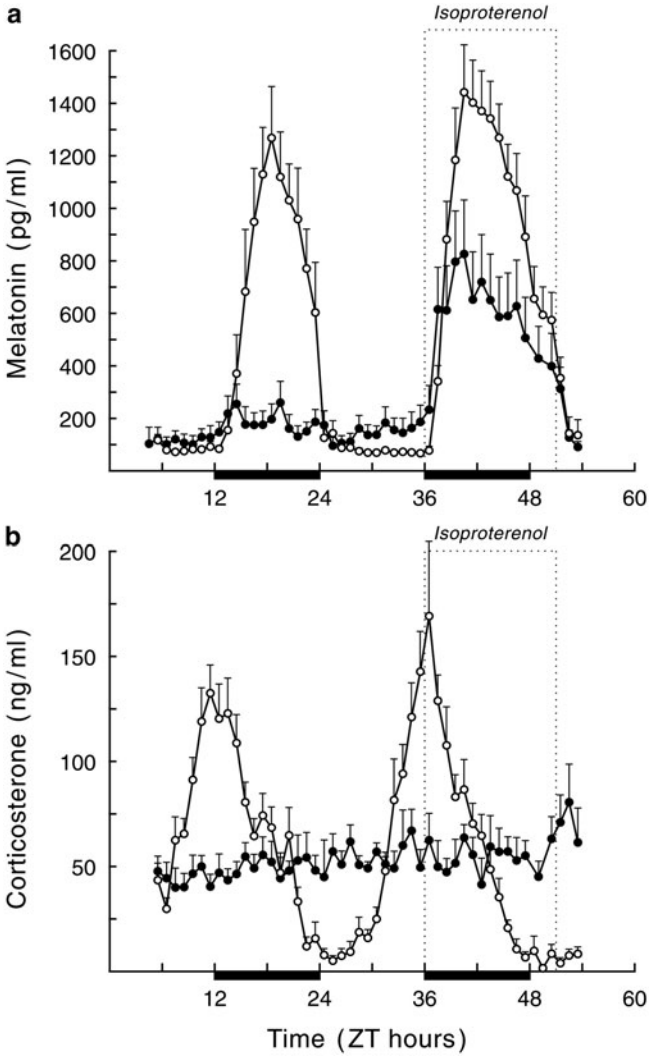

Fig. 2 Long-term secretion pattern of melatonin (**a**) and corticosterone (**b**) in intact *(open circles)* vs. SCN-lesioned (*closed circles*) rats measured by microdialysis in the pineal gland. A solution of isoproterenol was applied through the microdialysis probe in order to artificially stimulate the pineal gland and in this way check its capacity to release melatonin. The graphs represent mean data (±SEM) of eight intact and SCN-lesioned rats. (**a**) Note that the relatively low melatonin levels measured in SCN-lesioned animals increase after isoproterenol perfusion, showing (1) that the pineal is able to synthesise melatonin and (2) that the probes were correctly implanted in the gland

inhibitory and stimulatory SCN inputs, respectively, to regions of the preoptic area involved in the control of the sleep/wake rhythm (Sun et al. 2000, 2001). In addition, evidence of glutamate immunoreactivity within presynaptic boutons in the PVN (Van Den Pol 1991), as well as the demonstration of a specific glutamate

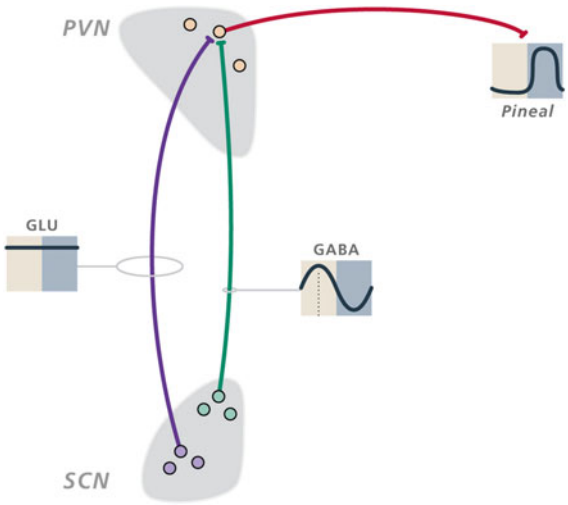

Fig. 3 Schematic presentation of the daily activity pattern of suprachiasmatic (SCN) populations of GABAergic and glutamatergic (GLU) neurons implicated in the autonomic control of the daily rhythm in pineal melatonin release. The continuous excitatory input to the sympathetic pre-autonomic neurons in the PVN from the glutamatergic SCN neurons only results in an actual activation of this neuron when the inhibitory GABAergic inhibition from the SCN is absent, i.e. the GABAergic SCN neurons function like a kind of traffic light, permitting the stimulatory input to the pre-autonomic neuron to become 'visible or noticeable' only when the GABAergic neurons permit so

release from the SCN onto (pre-autonomic) PVN neurons (Csaki et al. 2000; Cui et al. 2001; Hermes et al. 1996), shores up the idea of a glutamatergic SCN input to the PVN as well. Indeed, blocking glutamatergic transmission within the PVN at night by bilaterally infusing the *N*-methyl-D-aspartate receptor-specific glutamate antagonist, MK-801, significantly diminished melatonin levels, thus providing evidence that glutamatergic transmission within the PVN is a key player in the stimulation of melatonin at night (Perreau-Lenz et al. 2004).

In sum, the daily rhythm in plasma melatonin concentration is generated by a combination of stimulatory and inhibitory SCN outputs. The pre-autonomic PVN neurons that are in charge of the sympathetic input to the pineal gland are controlled by a combination of glutamatergic and GABAergic inputs from the SCN. The circadian and light-induced daytime activity of the GABAergic SCN projections to the PVN ensures low melatonin levels during the light period. The nocturnal arrest of the inhibitory GABAergic inputs, combined with the continuously active glutamatergic inputs, enables the pre-autonomic PVN to become active again and start a new period of melatonin synthesis and release (Fig. 3). To further define the subpopulations of SCN neurons responsible for these inhibitory and stimulatory signals, we used a combination of two different experimental paradigms, i.e. an 8-h advance of the L/D-cycle and a time-restricted feeding regime (Drijfhout et al. 1997; Kalsbeek et al. 2000a). From the results of these experiments, it became clear

that there is a small subset of *Per1*- and *Per2*-expressing neurons located in the central part of the SCN that is responsible for the nocturnal stimulation of melatonin release during the dark period (Kalsbeek et al. 2011). We propose that these neurons provide the necessary glutamatergic input to the PVN. In addition, an absence of *Per1* and *Per2* expression in the dorsal part of the SCN also seems a necessary prerequisite in order for melatonin levels to increase. We hypothesise that it is the 'activity' of these dorsal SCN neurons (and their sustained release of GABA) in the shifted animals that inhibits the pre-autonomic neurons in the PVN and prevents the reappearance of a new melatonin peak in the shifted dark period.

5 The Daily Rhythm in Luteinising Hormone Release

The SCN is important not only for the control of the daily rhythm in HPA axis and pineal gland activity but probably also for other hormonal axes, such as the hypothalamic–pituitary–gonadal (HPG) axis. Evidently, there is a clear relation between the mammalian biological clock and many aspects of reproduction: for example, the temporal organisation of pulsatile activity in the HPG axis is essential for the menstrual cycle. Lesion studies have shown that there are two brain structures that are indispensable for generating the preovulatory surge of LH: the MPOA, which contains a dense concentration of oestrogen receptors necessary for the positive oestrogen feedback, and the SCN, which provides the timing signal for the LH surge on the day of pro-oestrus. Early anatomical studies have already indicated a dense VP innervation in the MPOA, which probably derives from the SCN because it was not sensitive to gonadal hormones (Hoorneman and Buijs 1982; De Vries et al. 1984). Later studies showed that oestrogen receptor-containing neurons in the MPOA receive direct synaptic contacts from SCN fibres that probably contain VP as a neurotransmitter (De La Iglesia et al. 1995; Watson et al. 1995) and that VP receptor mRNA is expressed in MPOA neurons (Ostrowski et al. 1994; Funabashi et al. 2000a). In addition, some early studies by Södersten et al. (1983, 1985, 1986) indicated an interesting relationship between female sexual behaviour and SCN-derived VP, although at that time the effect could not be localised to a specific SCN target area. We hypothesised that the MPOA functions as an intermediate brain area for the transmission of circadian information from the SCN to the HPG axis, comparable to the intermediate function of the subPVN and DMH in the transmission of circadian information to the HPA axis. Indeed, an increase in extracellular VP levels brought about by reverse microdialysis in the MPOA of SCN-intact animals had a stimulatory effect on the LH surge, whereas it did not affect plasma corticosterone levels (Palm et al. 2001). The stimulatory effect of VP was restricted to a specific time period that coincided with the sensitive time window for a daily neuronal signal prior to the LH surge (Everett and Sawyer 1950), and also with the peak of VP secretion by SCN neurons. The important role of SCN-derived VP in the initiation of the LH surge was further emphasised by our experiments in SCN-lesioned animals. The complete absence of

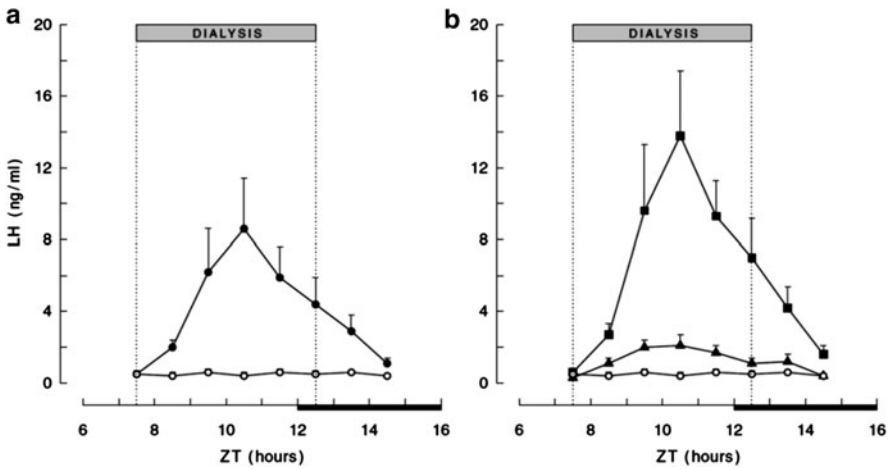

Fig. 4 Concentrations of plasma LH in SCN-lesioned, OVX + E animals. (**a**) Vasopressin-treated animals (closed symbols; $n = 9$) or vehicle-treated control animals (*open symbols*; $n = 6$), i.e. both vehicle-treated and vasopressin-treated groups consist of SCN-lesioned, OVX + E animals. In (**b**) the vasopressin-treated animals are divided in animals with a large SCN lesion (*filled triangles*; $n = 4$) and animals with a small SCN lesion (*filled squares*; $n = 5$). The smaller amount of LH released in the animals with the largest lesions probably is caused by damaged GnRH fibres travelling from the preoptic area to the median eminence, as many of these fibres travel through the perichiasmatic area bordering the SCN. Vasopressin was administered to the medial preoptic area (MPOA) via retrodialysis. The *hatched bar* represents the period of microdialysis with vasopressin; the *black bar* represents the dark period

any circadian output from the SCN induces basal, non-fluctuating LH levels, but a 2-h administration of VP in the MPOA is sufficient to reinstate a complete LH surge that is comparable to the oestrogen-induced surges in SCN-intact animals, both in shape and in amplitude (Palm et al. 1999; Fig. 4). Therefore, in our view, the high VP secretion by SCN terminals in the MPOA, occurring during the sensitive time window prior to the surge, is the circadian signal essential for the generation of an LH surge. Using completely different experimental setups, a similar conclusion was reached by Funabashi et al. (2000b) and Miller et al. (2006).

A key neuropeptide in the link between the SCN and the GnRH neurons is kisspeptin. Humans and mice lacking the kisspeptin receptor, Kiss1R (formerly known as GPR54), display hypogonadotropic hypogonadism, a condition characterised by severely impaired pubertal maturation and reproductive function due to deficient GnRH secretion (Messager 2005). Kisspeptin neurons are mostly concentrated in two discrete regions of the hypothalamus (1) rostral from the MPOA in the anteroventral periventricular nucleus (AVPV) and the rostral periventricular nucleus (PeN) and (2) arcuate nucleus in the caudal hypothalamus (Mikkelsen and Simonneaux 2009). Unlike GnRH neurons, kisspeptin-expressing neurons in the AVPV/PeN do express the alpha form of the oestrogen receptor

(ER-alpha), the subtype known to mediate the positive oestrogen feedback. Moreover, the Kiss1R is expressed in GnRH neurons (Khan and Kauffman 2011). The kisspeptin neurons thus emerge as an important link in the connection between the SCN and the LH surge. Indeed, VP-containing neurons from the SCN have been found to synapse on kisspeptin neurons. In addition, kisspeptin neurons in the AVPV/PeN express the VP receptor subtype V1a (Vida et al. 2010; Williams et al. 2011), while VIP projections to the kisspeptin neurons are scarce (Vida et al. 2010).

Another indirect connection via which the SCN could control the LH surge might involve RF-amide-related peptide (RFRP), also known as gonadotropin-inhibitory hormone (GnIH). RPRF-3-containing neurons are exclusively found in the DMH, which is one of the prime target areas of the SCN. RPRF-3 neurons express the ER-alpha and project heavily to the GnRH neurons in the MPOA. More direct evidence for a role of RFRP in the circadian regulation of the LH surge comes from 'splitting' experiments. De la Iglesia et al. (2003) had already shown that oestrogen-treated split females show an alternating activity of the left and right SCN, which went hand-in-hand with an activation of only the ipsilateral population of GnRH neurons. Later it was shown that the population of RFRP neurons in the DMH ipsilateral to the active half of the SCN shows a lower activity at the same time (Gibson et al. 2008).

Apart from this indirect control of the SCN on the LH surge via the kisspeptin neurons, direct projections from the SCN to the GnRH motor neurons, although sparse, have also been reported. Light microscopical (LM) studies, using double-labelling for SCN transmitters and GnRH, in combination with SCN lesions and tracing of SCN efferents, showed VIP-containing fibres in apposition to a substantial portion of the GnRH neurons. After lesions of the SCN, well over 50 % of the LM VIP input on GnRH neurons appeared to be derived from this nucleus (Van der Beek et al. 1993). At the ultrastructural level, too, synaptic interactions between VIP fibres and GnRH neurons were observed (Van der Beek 1996). Using immunocytochemistry for c-Fos, a marker for cell activation, a preferential activation during the initial stage of the LH surge was found of those GnRH neurons that are innervated by VIP-containing fibres (Van der Beek et al. 1994). Remarkably, these direct projections seem to be mainly VIPergic. Possibly the VIP-containing SCN projections to the GnRH neurons are involved in the transmission of the acute effects of light on the HPG axis (Van Der Beek 1996). Apposition of VP-containing fibres to GnRH neurons, although abundantly present in this area, was not observed (Van der Beek et al. 1993). The existence of a direct connection between the SCN and the GnRH system was further established by experiments using anterograde tracing and immunocytochemistry visualising GnRH at the light and electron microscopical level (Van der Beek 1996).

All in all, the circadian control of the HPG axis, using both direct and indirect connections, seems very much comparable to that summarised above for the HPA axis.

6 The Daily Rhythm in Plasma Thyroid Hormone Concentrations

Surprisingly little is known, still, about the daily rhythmicity of the hypothalamo–pituitary–thyroid (HPT) axis. Although, the daily rhythmicity of plasma thyroid-stimulating hormone (TSH) is well known in humans, neuroanatomical tracing and lesion studies in rats have shed relatively little extra light on the relationship between the central biological clock and thyroid hormone metabolism. Firstly, using immunocytochemistry SCN fibres were seen to contact TRH neurons in the PVN, a connection that may form the anatomical basis for the daily rhythms in hypothalamic TRH mRNA content (Martino et al. 1985; Collu et al. 1977; Covarrubias et al. 1988, 1994) and plasma TSH. Secondly, neuroanatomical studies using the retrograde transneuronal viral tracer PRV revealed multi-synaptic neural connections between the hypothalamic SCN and the thyroid gland via sympathetic and parasympathetic outflow. In addition, pre-autonomic neurons in the PVN, including TRH immunoreactive neurons, were labelled after injection of the PRV tracer into the thyroid gland (Kalsbeek et al. 2000b). Frequent blood sampling via permanent cannulas revealed daily rhythms of TSH and thyroid hormones with peak levels during the first half of the light period and through levels in the early dark period, which is the reverse of the human rhythm. A second peak occurred during the middle of the dark period, although this was significant only for TSH (Rookh et al. 1979; Fukuda and Greer 1975; Ottenweller and Hedge 1982; Jordan et al. 1980). A thermic ablation of the SCN completely eliminated the diurnal peak in circulating TSH and thyroid hormones, showing that the SCN drives the diurnal variation (Kalsbeek et al. 2000b). However, targeted hypothalamic infusions of SCN neurotransmitter agonists or antagonist, which had been so helpful in the above described studies on other hormonal axis, thus far have not disclosed any information on the SCN signals involved in the control of the daily HPT rhythm (unpublished data). A more recent study from our group showed a significant daily activity rhythm of the enzyme type 2 deiodinase (D2), which is the enzyme that deiodinates the prohormone thyroxine (T4) into the biologically active triiodothyronine (T3), in the pineal and pituitary gland and in the hypothalamus and neocortex. Ablation of the SCN abolished this rhythm in all brain areas studied (Kalsbeek et al. 2005). These results indicate that the bioavailability of T3 in various brain areas may show a diurnal rhythm that is driven by the SCN. However, the solid-phase liquid chromatography/tandem mass spectrometry (SPE LC-MS/MS) method—recently developed in our lab to determine thyroid hormones and their metabolites in tissue samples (Ackermans et al. 2012)—has not yet been applied to demonstrate this in brain tissue.

Using frequent blood sampling, a circadian pattern of TSH secretion was reported in humans in the early 1990s with low plasma TSH levels during the daytime, an increase in the late afternoon or early evening and a peak (the so-called nocturnal TSH surge) around the beginning of the sleep period. Plasma TSH decreases again during the later stages of sleep to reach daytime values after

morning awakening. In fact, the pronounced circadian TSH rhythm only became apparent after the inhibitory effect of sleep had been discovered (Allan and Czeisler 1994; Brabant et al. 1990). In addition to this diurnal rhythm, healthy human subjects show a clear ultradian rhythm with a pulse every 1–3 h first reported by Parker et al. (1976). Later studies using 10-min interval sampling, sensitive TSH assays and quantitative analysis confirmed that the ultradian TSH release follows a high-frequency (approx. 10 pulses per hour) and low-amplitude (0.4 mU/L) pulsatile pattern superimposed on the low-frequency and high-amplitude (1.0 mU/L) pattern of the circadian TSH rhythm. The regulatory mechanisms responsible for circadian and pulsatile TSH release in humans are incompletely understood. TSH secretion is controlled by the stimulatory action of the hypothalamic neuropeptide TRH in the PVN and the inhibitory action of central dopaminergic and somatostatinergic action, in addition to the negative hypothalamic and pituitary feedback action of the thyroid hormones T4 and T3. In spite of the clear diurnal variation in plasma TSH, circadian or sleep-related rhythms in plasma concentrations of the thyroid hormones T4 and T3 in humans are less obvious (Greenspan et al. 1986). Although this may reflect a molecular change in the TSH molecule with reduced bioactivity in the night period, altered sensitivity of the thyroid gland over the clock might be an alternative explanation as suggested by animal experimental studies (Kalsbeek et al. 2000b). On the other hand, neurologically complete cervical spinal injury did not disrupt the daily rhythmicity of TSH (or cortisol) secretion, whereas it did cause a complete loss of the plasma melatonin rhythm (Zeitzer et al. 2000).

Although there are no clear sex differences in the diurnal TSH and thyroid hormone rhythm (Roelfsema et al. 2009), contrary to what has been observed in rodents, there are several physiological (Behrends et al. 1998) and pathological conditions that alter the TSH rhythm. Bartalena et al. reported an absent nocturnal TSH surge in major depression (Bartalena et al. 1990) suggesting a role for hypothalamic TRH in the pathogenesis of HPT axis changes in depression. This was supported by the observation in a post-mortem study of markedly decreased TRH mRNA expression in the PVN of patients with major depression compared with subjects without psychiatric disease (Alkemade et al. 2003). A decreased or even absent nocturnal TSH surge was found to be present in a variety of additional nonthyroidal illnesses, occurring independently of plasma thyroid hormone concentrations or pituitary responsiveness to TRH (Romijn and Wiersinga 1990), which again may point to a hypothalamic factor. Patients with critical illness who were treated in the intensive care unit for a prolonged period of time show markedly decreased TSH pulsatility with a completely absent nocturnal TSH surge and a decreased TSH pulse amplitude (Van Den Berghe et al. 1997). The decrease in pulsatile TSH secretion was related to the low serum T3 concentration, in keeping with the concept that reduced production of thyroid hormone during prolonged critical illness may have, at least in part, a neuroendocrine origin. This was confirmed by post-mortem investigation of the PVN of patients, whose serum thyroid hormone concentrations had been assessed just before death, showing decreased TRH mRNA expression in patients with prolonged critical illness in close correlation with serum TSH (Fliers et al. 1997). Additional support for a

major role for hypothalamic TRH in the decreased TSH release during critical illness came from clinical studies in the intensive care unit (ICU) setting and showed that the continuous administration of TRH to patients with prolonged critical illness partially restored the serum concentrations of TSH as well as those of T4 and T3 (Van Den Berghe et al. 1998; Fliers et al. 2001).

In addition to critical illness, the nocturnal TSH surge is diminished in various endocrine pathologies, including hypercortisolism (Bartalena et al. 1991). A recent study in patients with primary hypothyroidism reported a persisting diurnal TSH rhythm with an earlier acrophase in most patients, while both basal and pulsatile TSH secretion rates were increased based on increased burst mass with unaltered burst frequency (Roelfsema et al. 2010). In central hypothyroidism, a lower absolute and relative nocturnal rise in TSH was observed (Adriaanse et al. 1992). Likewise, physiological conditions may affect the TSH rhythm. Clear examples are the decreased nocturnal TSH surge during fasting in association with decreased TSH pulse amplitude and unaltered TSH pulse frequency (Romijn et al. 1990) and the increased TSH surge during the first night of sleep deprivation (Goichot et al. 1998).

7 The Daily Rhythm in Plasma Glucose and Glucoregulatory Hormones

On the basis of a series of retrograde viral tracing studies from adipose tissue (both brown and white), pancreas, stomach and the heart and intestines, a similar SCN control as just discussed for the adrenal gland, pineal gland and ovaries may apply for other peripheral tissues as well (Buijs et al. 2001; Bartness et al. 2001; Scheer et al. 2001; Kreier et al. 2006), in particular for tissues involved in energy metabolism. On this basis we hypothesised that part of the action of the SCN to prepare our bodies for the alternating periods of sleep and wakefulness would be through its connections with the hypothalamic pre-autonomic neurons to control the daily setting of the sympathetic–parasympathetic balance of autonomic inputs to these peripheral organs. Indeed, in a first series of viral tracing experiments, we were able to show a clear separation of the pre-autonomic neurons that control the sympathetic and parasympathetic branch of the autonomic nervous system, up to the level of the second-order neurons in the hypothalamus (La Fleur et al. 2000; Buijs et al. 2001; Kalsbeek et al. 2004). Subsequently, we investigated whether one single group of neurons within the biological clock would be dedicated to the control of these sympathetic and parasympathetic pre-autonomic neurons, in other words, whether also within the SCN there is a clear separation of neurons controlling the sympathetic and parasympathetic branches of the autonomic nervous system. Using a combination of double viral tracing and selective organ denervation, we were able to demonstrate that the segregation of pre-sympathetic and pre-parasympathetic neurons already starts at the level of the SCN (Buijs et al. 2003). This high level of

differentiation puts the SCN in a unique position to balance the activity of both ANS branches according to the time of day. However, although these neuroanatomical data provide a nice blueprint for the possible SCN control of energy metabolism and the autonomic balance, the big question remains whether, and if so, to what extent this neuroanatomical blueprint has any functional significance.

To investigate whether the SCN control of the parasympathetic branch of the ANS is comparable to the one described above for the sympathetic branch, we then focused our attention on the daily rhythm in plasma glucose concentrations. Maintaining a constant blood glucose level is essential for normal physiology in the body, particularly for the central nervous system (CNS), as the CNS can neither synthesise nor store the glucose which is required as an energy source for the brain. The liver plays a pivotal role in maintaining optimum glucose levels by balancing glucose entry into, and removal from, the circulation. From a hypothalamic and chronobiological point of view, glucose production by the liver is especially interesting because of the clear involvement of both the sympathetic and parasympathetic input to the liver in glucose metabolism (Shimazu 1987; Nonogaki 2000; Puschel 2004) and the strong circadian control of (glucose) metabolism in the liver (Kita et al. 2002; Akhtar et al. 2002; Oishi et al. 2002). Using local intrahypothalamic administration of GABA and glutamate receptor (ant)agonists, we explored the contribution of changes in ANS activity to the daily control of plasma glucose and plasma insulin concentrations. The daily rhythm in plasma glucose concentrations turned out to be controlled according to a mechanism very much similar to the mechanism described above for the SCN control of the daily rhythm in melatonin release (Fig. 5), i.e. a combination of rhythmic GABAergic inputs and continuous glutamatergic stimulation onto liver-dedicated sympathetic preautonomic neurons in the PVN (Kalsbeek et al. 2004, 2008a). The major difference between the liver-dedicated and pineal-dedicated pre-autonomic neurons seems to be the timing of the GABAergic inputs. In the case of the pineal-dedicated preautonomic neurons, this inhibitory input is present during the major part of the light period with an acrophase around ZT6, whereas for the liver-dedicated preautonomic neurons, the acrophase of the GABAergic inhibition is somewhere around ZT2. Surprisingly, no clear evidence was found for an involvement of the parasympathetic branch of the ANS, as our previous denervation studies clearly showed the daily plasma glucose rhythm to be disrupted, also in parasympathetic liver-denervated animals (Cailotto et al. 2008).

Plasma glucose concentrations are the result of a glucose *influx* from the gut and liver and of glucose *efflux* by its uptake in brain, muscle and adipose tissue. To investigate in more detail by which glucoregulatory mechanism the just described SCN output mechanism contributes to the increased plasma glucose concentrations at awakening, we first performed a series of intravenous glucose tolerance and insulin sensitivity tests in rats. To our surprise these studies revealed that glucose tolerance and insulin sensitivity peak at the onset of the dark period (La Fleur 2003). The rise in plasma glucose concentrations at the end of the sleep period could thus not be explained by a diminished glucose uptake at this time of the L/D-cycle. These studies also indicated that glucose production should increase at the

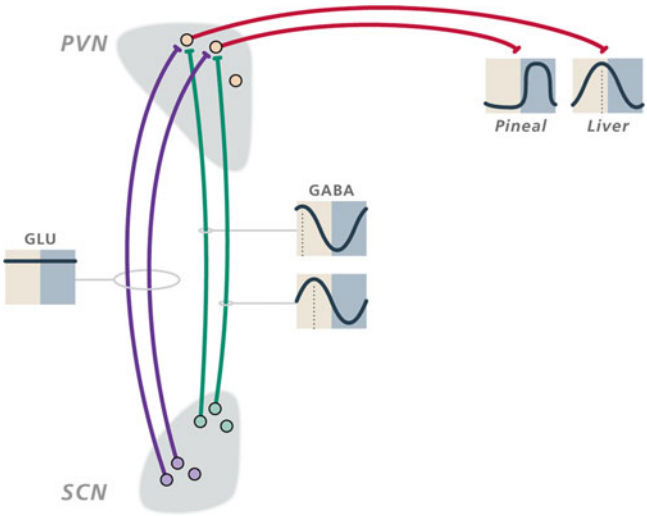

Fig. 5 Schematic presentation of the daily activity pattern of suprachiasmatic (SCN) populations of GABAergic and glutamatergic (GLU) neurons implicated in the autonomic control of the daily rhythms in pineal melatonin release and hepatic glucose production. For the control of the daily rhythms in melatonin release and glucose production, the SCN seems to rely on a uniform mechanism of continuous glutamatergic and rhythmic GABAergic inputs to the sympathetic pre-autonomic neurons. The difference in the timing of the acrophase for the melatonin and glucose production, however, indicates that separate populations of GABAergic neurons should be in contact with the pineal-dedicated and liver-dedicated pre-autonomic neurons, i.e. separate traffic lights for the pineal and the liver. In line with the idea of such a highly differentiated SCN, viral tracing studies have shown that separate neurons in the SCN are in contact with abdominal and subcutaneous adipose compartments (Kreier 2005)

end of the sleep period, to compensate for the increased glucose uptake and to explain the increased plasma glucose concentrations. We went on to combine hypothalamic infusions with systemic infusion of a stable glucose isotope. The use of the stable glucose isotope enabled us to distinguish between changes in glucose production and glucose uptake. These experiments showed that a pronounced increase in hepatic glucose production was caused by the administration of bicuculline (a GABA-A receptor antagonist) in the perifornical area lateral to the DMH and that orexin- (but not melanin-concentrating hormone (MCH)-) containing neurons in this area were strongly activated (Yi et al. 2009). Subsequent studies revealed that the hyperglycemic effect of bicuculline could be prevented by the concomitant ICV administration of an orexin antagonist and that orexin fibres impinge upon sympathetic preganglionic neurons in the IML of the spinal cord that project to the liver (Van Den Top et al. 2003; Yi et al. 2009). Earlier we had demonstrated that the hyperglycemic effect of a focal blockade of GABAergic transmission was very much dependent on the time of day (Kalsbeek et al. 2008a), indicating SCN control. Indeed, using an approach very similar to ours, Alam et al. (2005) had already demonstrated that perifornical orexin neurons are subject to an

increased endogenous GABAergic inhibition during sleep. In view of the pronounced day/night rhythm in orexin release (Zeitzer et al. 2003; Zhang et al. 2004), we hypothesised that orexin is the main connection between the biological clock and the daily rhythm in plasma glucose concentrations. To test this hypothesis, we measured the rate of glucose appearance (Ra) in ad libitum fed animals during the second half of the light period and the first hours of the dark period, i.e. during the ascending phase of the daily rhythm in plasma glucose. We combined these measurements with the ICV infusion of an orexin antagonist or vehicle. The results of this experiment pointed to an important role for the orexin system in the control by the biological clock over daily glucose homeostasis, as the ICV orexin antagonist prevented the daily dusk time increase in glucose appearance. The perifornical orexin neurons thus seem to transduce the rhythmic GABA and glutamatergic signals emanating from the SCN into a daily activation of the sympathetic input to the liver, which results in an increased hepatic glucose production at the end of the sleep period in anticipation of a new period of wakefulness (Fig. 6). Remarkably, a recent study by Shiuchi et al. (2009) demonstrated that orexin is able to stimulate glucose uptake in muscle via the ventromedial nucleus of the hypothalamus (VMH) and the sympathetic nervous system. Thus, orexin might be an important link in the SCN-controlled concomitant increase of both glucose production and glucose uptake at the onset of the activity period (La Fleur 2003). Together, these results indicate that, due to a disinhibition of the orexin system at the end of the light period, the SCN not only promotes arousal but also causes an increase of endogenous glucose production to ensure adequate concentrations of plasma glucose when the animal wakes up. Other studies made it very likely that the rhythmic activity of the orexin system is also involved in the increased activity of the cardiovascular system at awakening (Shirasaka et al. 1999; Zhang et al. 2009).

As has become evident from the daily variation in meal-induced insulin responses (Kalsbeek and Strubbe 1998), intestinal glucose uptake (Houghton et al. 2006), respiratory functioning (Bando et al. 2007) and markers of cardiac vagal activity (Burgess et al. 1997; Hilton et al. 2000; Scheer et al. 2004a), the parasympathetic branch of the autonomic nervous system too is governed by the circadian timing system. Using intra-hypothalamic infusions, we were able to show that the daily changes in the activity of the parasympathetic pre-autonomic neurons also involve a combination of GABAergic and glutamatergic inputs (Kalsbeek et al. 2008a). The inhibition of pre-autonomic neurons, both sympathetic and parasympathetic, by a daily rhythm in GABA release from SCN efferents to the PVN turned out to be a general principle. However, a major difference between the circadian control of parasympathetic and sympathetic pre-autonomic neurons appears to be the origin of the excitatory glutamatergic inputs. SCN-lesion studies proved that the excitatory input to the sympathetic pineal-dedicated pre-autonomic neurons was derived from the SCN neurons (Perreau-Lenz et al. 2003), but also that the glutamatergic inputs to the parasympathetic pancreas-dedicated pre-autonomic

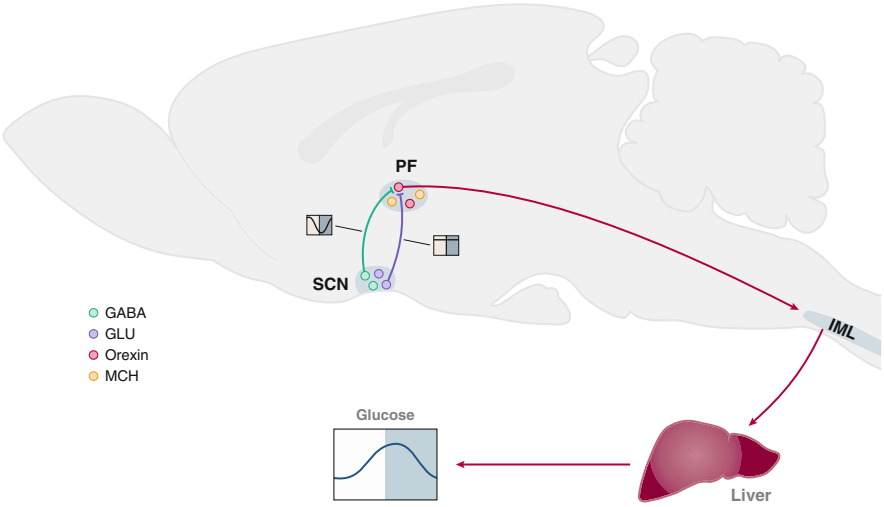

Fig. 6 Midsagittal view of the rat brain with a hypothesised presentation of the involvement of orexin neurons in the autonomic control of the daily rhythm of hepatic glucose production. (1) The orexin-containing neurons in the perifornical area (PF) are innervated by both glutamatergic and GABAergic projections from the biological clock (SCN). During the main part of the light period, activation of the orexin neurons by the excitatory glutamatergic inputs is prevented by releasing the inhibitory neurotransmitter GABA (the daily activity pattern of these inputs is indicated by the *lines* in the *yellow/blue boxes* aside the projections). The circadian withdrawal of the GABAergic input allows the orexin neurons to become active at the onset of darkness. (2) Subsequently, the excitatory effect of orexin on the preganglionic neurons in the IML of the spinal cord will (3) activate the sympathetic input to the liver and result in increased hepatic glucose production. Orexin also stimulates glucose uptake in skeletal muscle via action in the VMH and mediated through the sympathetic nervous system (Shiuchi et al. 2009); but, as it is not clear yet how the message is propagated from the VMH to the autonomic nervous system, this action has not been incorporated in this scheme

neurons cannot be derived from SCN neurons (Strubbe et al. 1987). At present, it is not yet clear from which extra-SCN source the glutamatergic inputs to the parasympathetic pancreas-dedicated pre-autonomic neurons originate, but likely candidates are the VMH and arcuate nucleus (Fig. 7).

8 Daily Rhythms in Plasma Adipokines

Adipose tissue composes one of the largest organs in the body. It can make up from 5 % of body weight in lean men to over 50 % in the morbidly obese. In mammals, two major, functionally different, types of adipose tissue have been described: brown adipose tissue (BAT) and white adipose tissue (WAT). BAT and WAT share the ability to store lipids as triglycerides, but use them for different purposes. BAT produces heat and plays an important role in non-shivering thermogenesis.

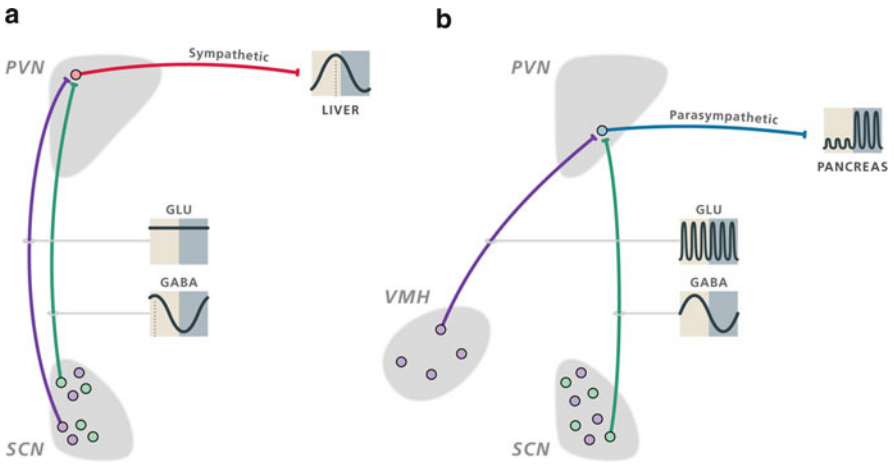

Fig. 7 Schematic presentation of the daily activity pattern of hypothalamic populations of GABAergic and glutamatergic (GLU) neurons implicated in the autonomic control of the daily rhythms in hepatic glucose production (*left-hand side*) and feeding-induced insulin release (*right-hand side*). Similar to the previously proposed circadian control of the *sympathetic* pre-autonomic neurons (*left-hand side*), also the circadian control of the *parasympathetic* pre-autonomic neurons seems to rely on a combination of glutamatergic and GABAergic inputs (*right-hand side*). However, whereas for both types of neurons the rhythmic GABAergic input is derived from the SCN, the sources of glutamatergic input seem to be different, i.e. SCN for the *sympathetic* pre-autonomic neurons and extra-SCN for the *parasympathetic* ones. In the figure the VMH is indicated as the most likely origin of the glutamatergic input, but at present experimental evidence is lacking for this proposition. Moreover, whereas the glutamatergic input from the SCN to the *sympathetic* pre-autonomic neurons is proposed to be continuous, the glutamatergic input from the VMH to the *parasympathetic* pre-autonomic neurons is proposed to be dependent on feeding activity

WAT, besides functioning as mechanical and thermal protection of vital organs and as an important long-term energy store, secretes several proteins that influence processes as diverse as haemostasis, blood pressure, immune function, angiogenesis and energy balance (Christodoulides et al. 2009).

Obesity is characterised by excessive accumulation of triglycerides in adipose tissue, determined by a net balance of fatty acid uptake and release in favour of fat storage over fat mobilisation. The rich innervation of adipose tissue by sympathetic fibres is well known, and activation of these fibres is associated with enhanced lipolysis (Weiss and Maickel 1968). Until a few years ago, it was thought that parasympathetic innervation of adipose tissue did not occur and that lipogenesis was merely controlled by hormones, the mass action of free fatty acids and sympathetic withdrawal. In view of the importance of this balance between lipogenesis and lipolysis, and the capacity of the SCN to control the sympathetic/parasympathetic balance in other organs, we reinvestigated the existence of parasympathetic input to adipose tissue. This would allow us to test the possibility of SCN control of this lipogenesis/lipolysis balance through the autonomic nervous system. Indeed, as previously reported by others (Bamshad et al. 1998), at first we

found only very sparse parasympathetic input to white adipose tissue. However, combining the viral tracing technique with a prior selective sympathetic denervation of the targeted fat pad resulted in pronounced labelling of the parasympathetic motor neurons in the brainstem (Kreier et al. 2002). It is not clear what causes this increased visibility of the parasympathetic input, but one possibility is that the parasympathetic fibres are only exposed to the virus when the more active sympathetic fibres have been removed, as previous studies have shown that viral tracing can be modulated by neuronal activity (Lee and Erskine 2000). Although parasympathetic innervations of WAT had not been replicated by others at this stage, these observations provided the neuroanatomical substrate for earlier pharmacological observations in human microdialysis studies that showed cholinergic effects on lipolysis (Andersson and Arner 1995) and the more recent identification of functional acetylcholine receptors in rat adipocytes (Liu et al. 2004; Yang et al. 2009). In addition, our own functional studies provided clear evidence for an anabolic function of this parasympathetic innervation of adipose tissue. Euglycemic hyperinsulinemic clamp studies revealed a >30 % reduction in the insulin-mediated uptake of glucose and free fatty acids (FFAs) in adipose tissue as a result of selective removal of its parasympathetic input. Moreover, without parasympathetic input, the activity of the catabolic enzyme hormone-sensitive lipase (HSL) increased by 51 % in the denervated adipose tissue (Kreier et al. 2002). Follow-up studies using two different PRV tracers and selective denervation of the adipose tissue showed the presence of both 'sympathetic' and 'parasympathetic' adipose neurons in the hypothalamus, including the SCN (Kreier 2005). These results thus provide clear evidence that the SCN may use the ANS also to enforce its day/night rhythms upon the endocrine and metabolic functioning of adipose tissue.

As indicated above, white adipose tissue also plays a central role in the regulation of energy metabolism, mainly via the secretion of factors (adipokines) that regulate appetite, food intake, glucose disposal and energy expenditure (Wang et al. 2008). Adipokines are secreted by adipocytes and/or the stromavascular fraction of WAT. Originally the term adipokine was proposed to describe cytokines secreted from adipocytes specifically. However, as many cell types in adipose tissue have been found to secrete proteins and other proteins besides cytokines are being produced, the term adipokine is now widely used to describe proteins secreted from adipose tissue (Stryjecki and Mutch 2011; Wang et al. 2008). Extensive reviews on the metabolic functions of adipokines have been published in recent years (Halberg et al. 2008; Trujillo and Scherer 2006; Poulos et al. 2010; Maury and Brichard 2010). Like most other tissues, WAT gene expression shows circadian rhythmicity (Ando et al. 2005; Ptitsyn et al. 2006). Indeed, both fat deposition by the key enzyme lipoprotein lipase (LPL) and fat mobilisation by HSL show a clear daily rhythm in the white adipose tissue of humans and laboratory animals (Hems et al. 1975; Cornish and Cawthorne 1978; Bergö et al. 1996; Hagström-Toft et al. 1997; Benavides et al. 1998). Moreover, also the circulating plasma levels of a number of adipokines, including leptin, as well as their adipose mRNA levels show clear day/night rhythms.

Leptin is a hormone secreted by adipose tissue in proportion to body fat amount and relays fat storage information to the brain. High levels of leptin signal satiety and reduce food intake, whereas low levels of leptin stimulate food intake (Schwartz et al. 2000). The discovery that plasma leptin helps to regulate body weight through its hypothalamic effects on food intake and energy expenditure represented a major breakthrough in our understanding of the neuroanatomical and molecular components of the systems involved in energy homeostasis (Farooqi 2011). For the discovery of this previously unknown endocrine system, Coleman and Friedman received the Albert Lasker Award for Basic Medical Research in 2010 (Flier and Maratos-Flier 2010).

Many studies by now have shown that plasma levels of leptin fluctuate over the day and night (Simon et al. 1998; Kalsbeek et al. 2001; Gavrila et al. 2003; Shea et al. 2005). It has been shown that plasma leptin levels are regulated not only by fat mass and the biological clock but also by feeding and that long periods of fasting eliminate the leptin rhythm (Elimam and Marcus 2002). However, under constant and continuous feeding conditions, a circadian rhythm in leptin persists, indicating a role for the circadian clock in regulating leptin levels during fed conditions (Simon et al. 1998; Kalsbeek et al. 2001). In healthy volunteers, misalignment between behaviour and endogenous circadian timing leads to lower overall leptin levels (Scheer et al. 2009), suggesting that leptin responds to the endogenous circadian clock independent of behavioural factors such as feeding. Although SCN lesions eliminate leptin circadian rhythmicity (Kalsbeek et al. 2001), cultured adipocytes still show rhythmic leptin mRNA expression, implying regulation by an endogenous clock within the adipocytes (Brown and Azzi 2013; Bass 2013; Otway et al. 2009). In addition to being regulated by the clock, leptin may also serve as an input factor for the biological clock. The leptin receptor is expressed in SCN cells, and in vitro leptin can phase-advance the SCN (Prosser and Bergeron 2003). In sum, leptin is a pivotal factor in the interplay between feeding cues, metabolic state and circadian timing.

Besides leptin also several other adipokines show a significant day/night rhythm. Adiponectin is an adipokine that is involved in glucose and lipid metabolism by increasing fatty acid oxidation and potentiating insulin-mediated inhibition of hepatic gluconeogenesis, thus promoting insulin sensitivity (Barnea et al. 2010). Interestingly, although adiponectin is produced by adipose tissue, its serum levels and WAT gene expression decrease in obesity and in animals fed a high-fat diet (Barnea et al. 2010; Boucher et al. 2005; Turer et al. 2011). Both in vitro and in vivo, adiponectin has a significant day/night rhythm (Scheer et al. 2010; Barnea et al. 2010; Otway et al. 2009; Gavrila et al. 2003; Garaulet et al. 2011), with a trough at night for humans, and during the day for rats (Scheer et al. 2010; Oliver et al. 2006). This rhythm is not driven by feeding/fasting cycle in lean men (Scheer et al. 2010). $Clock^{\Delta 19}$ mutant mice that retain melatonin rhythmicity ($Clock^{\Delta 19}$ + MEL) show increased eWAT adiponectin gene expression, which may contribute to the improved insulin resistance that is found in $Clock^{\Delta 19}$ + MEL mice compared to $Clock^{\Delta 19}$ mice (Kennaway et al. 2011).

Resistin is a cytokine that is produced in WAT (adipocytes in rodents, macrophages in human) and is a potential mediator of type 2 diabetes and cardiovascular disease (Ando et al. 2005; Oliver et al. 2006; Rajala et al. 2004; Schwartz and Lazar 2011) with higher expression rates in omental versus subcutaneous WAT of obese female subjects (Fain et al. 2003). Resistin mRNA expression is rhythmic in several WAT compartments in rats, with a peak in the late dark/early light phase (Oliver et al. 2006). Resistin is downregulated by fasting and upregulated by (re-) feeding (Oliver et al. 2006). However, WAT gene expression levels of resistin are decreased in obese and high-fat-diet-fed mice (Boucher et al. 2005). Rotating shift workers have elevated plasma levels of resistin compared to day work controls (Burgueño et al. 2010).

Visfatin is a multifunctional protein produced by adipose tissue, but also by skeletal muscle, liver, and immune cells, and is also known as nicotinamide phosphoribosyltransferase (Nampt) or pre-B-cell colony-enhancing factor (PBEF). Circulating visfatin levels have been reported to be elevated in type 2 diabetes and obesity (Fukuhara et al. 2005; Chen et al. 2006; Hallschmid et al. 2009; Berndt et al. 2005). In rodents the expression of visfatin shows a circadian rhythm in WAT, as well as in adipocytes and hepatocytes (Ando et al. 2005; Ramsey et al. 2009), but also circulating levels in human plasma show a clear daily rhythm (Benedict et al. 2012). Since plasma visfatin levels also seem to be affected by sleep duration (Hayes et al. 2011; Benedict et al. 2012), visfatin has been proposed to have a regulatory role in the deleterious metabolic effects of sleep deprivation.

9 Future Perspective

It is now generally accepted that the SCN is the principal neural structure that mediates circadian rhythms in mammals, including man. A key question at this stage is whether a strengthening of the SCN signal could alleviate pathologies such as insulin resistance, obesity and hypertension. An interesting example of the possible utility of this approach was provided by an experiment investigating this in terms of alleviating the increased blood pressure in hypertensive patients. A randomised, double-blind, placebo-controlled crossover study was conducted in which 16 men with untreated essential hypertension were treated with oral melatonin (2.5 mg daily; 1 h before sleep) for 3 weeks. Repeated melatonin administration reduced ambulatory systolic and diastolic blood pressure by 6 and 4 mmHg, respectively (Scheer et al. 2004b).

A second example is provided by another ‘experiment of nature’, i.e. ageing: a marked decrease in the number of VP-containing neurons was observed in subjects between 80 and 100 years of age (Swaab et al. 1985; Harper et al. 2008). Moreover, a flattening of the daily rhythm in SCN VP abundance was already observed in subjects >50 years of age (Hofman and Swaab 1994). In addition, an age-related increase in abdominal obesity and type 2 diabetes is well known. As with the daily

melatonin treatment in hypertensive patients, long-term treatment of elderly with whole-day bright light during the day period improved cognitive and noncognitive symptoms of dementia (Riemersma-Van Der Lek et al. 2008), although at this stage no metabolic parameters were investigated.

Interestingly, the loss of immunoreactivity for SCN neurotransmitters during ageing and hypertension is probably not due to a loss of neurons, but to a decreased activity of these neurons. Therefore, an important way to revitalise a flattened and disorganised SCN output might be to enhance the rhythmic input signals to the SCN. Thus, daily melatonin treatment and daily light treatment may help to improve circadian rhythms in behaviour by an enhancement of biological clock functioning. A third treatment strategy might be daily exercise, which is indeed a very effective way to improve glucose tolerance. Although the experiments described above may yield therapeutic strategies to counteract the negative health effects of a chronically desynchronised SCN output, they may not apply for shift workers, as here the circadian misalignment is in constant flux. During working days shift workers are compelled to shift their sleep/wake rhythm to meet the needs of work hours, but during days off they revert to a normal daytime activity schedule to meet the needs of social life. Therefore, future studies identifying the exact mechanisms of internal desynchronisation are justified if we are to propose behavioural strategies capable of minimising the adverse effects of circadian misalignment (Roenneberg et al. 2013).

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References

Ackermans MT, Kettelarij-Haas Y, Boelen A, Endert E (2012) Determination of thyroid hormones and their metabolites in tissue using SPE UPLC-tandem MS. Biomed Chromatogr 26(4): 485–490

Adriaanse R, Romijn JA, Endert E, Wiersinga WM (1992) The nocturnal thyroid-stimulating hormone surge is absent in overt, present in mild primary and equivocal in central hypothyroidism. Acta Endocrinol 126:206–212

Akhtar RA, Reddy AB, Maywood ES, Clayton JD, King VM, Smith AG, Gant TW, Hastings MH, Kyriacou CP (2002) Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. Curr Biol 12:540–550

Alam MN, Kumar S, Bashir T, Suntsova N, Methippara MM, Szymusiak R, McGinty D (2005) GABA-mediated control of hypocretin- but not melanin-concentrating hormone-immunoreactive neurones during sleep in rats. J Physiol 563:569–582

Alexander LD, Sander LD (1994) Vasoactive intestinal peptide stimulates ACTH and corticosterone release after injection into the PVN. Regul Pept 51:221–227

Alkemade A, Unmehopa U, Brouwer JP, Hoogendijk WJ, Wiersinga WM, Swaab DF, Fliers E (2003) Decreased thyrotropin-releasing hormone gene expression in the hypothalamic paraventricular nucleus of patients with major depression. Mol Psychiatry 8:838–839

Allan JS, Czeisler CA (1994) Persistence of the circadian thyrotropin rhythm under constant conditions and after light-induced shifts of circadian phase. J Clin Endocrinol Metab 79: 508–512

Andersson K, Arner P (1995) Cholinoceptor-mediated effects on glycerol output from human adipose tissue using in situ microdialysis. Br J Pharmacol 115:1155–1162
Ando H, Yanagihara H, Hayashi Y, Obi Y, Tsuruoka S, Takamura T, Kaneko S, Fujimura A (2005) Rhythmic messenger ribonucleic acid expression of clock genes and adipocytokines in mouse visceral adipose tissue. Endocrinology 146:5631–5636
Axelrod J (1974) The pineal gland: a neurochemical transducer. Science 184:1341–1348
Badura LL, Kelly KK, Nunez AA (1989) Knife cuts lateral but not dorsal to the hypothalamic paraventricular nucleus abolish gonadal responses to photoperiod in female hamsters (Mesocricetus auratus). J Biol Rhythms 4:79–91
Bamshad M, Aoki VT, Adkison MG, Warren WS, Bartness TJ (1998) Central nervous system origins of the sympathetic nervous system outflow to white adipose tissue. Am J Physiol 275:R291–R299
Bando H, Nishio T, van der Horst GT, Masubuchi S, Hisa Y, Okamura H (2007) Vagal regulation of respiratory clocks in mice. J Neurosci 27:4359–4365
Barassin S, Kalsbeek A, Saboureau M et al (2000) Potentiation effect of vasopressin on melatonin secretion as determined by trans-pineal microdialysis in the rat. J Neuroendocrinol 12:61–68
Bargman W (1943) Die epiphysis cerebri. In: Von MW (ed) Handbuch der Miskroskopischen Anatomie des Menschen. Springer, Berlin, pp 338–502
Barnea M, Madar Z, Froy O (2010) High-fat diet followed by fasting disrupts circadian expression of adiponectin signaling pathway in muscle and adipose tissue. Obesity 18:230–238
Bartalena L, Placidi GF, Martino E, Falcone M, Pellegrini L, Dell'Osso L, Pacchiarotti A, Pinchera A (1990) Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: dissociated behavior in untreated depressives. J Clin Endocrinol Metab 71:650–655
Bartalena L, Martino E, Petrini L, Velluzzi F, Loviselli A, Grasso L, Mammoli C, Pinchera A (1991) The nocturnal serum thyrotropin surge is abolished in patients with adrenocorticotropin (ACTH)-dependent or ACTH-independent Cushing's syndrome. J Clin Endocrinol Metab 72: 1195–1199
Bartness TJ, Song CK, Demas GE (2001) SCN efferents to peripheral tissues: implications for biological rhythms. J Biol Rhythms 16:196–204
Bass J (2013) Circadian clocks and metabolism. In: Kramer A, Merrow M (eds) Circadian clocks, vol 217, Handbook of experimental pharmacology. Springer, Heidelberg
Behrends J, Prank K, Dogu E, Brabant G (1998) Central nervous system control of thyrotropin secretion during sleep and wakefulness. Horm Res 49:173–177
Benavides A, Siches M, Llobera M (1998) Circadian rhythms of lipoprotein lipase and hepatic lipase activities in intermediate metabolism of adult rat. Am J Physiol 275:R811–R817
Benedict C, Shostak A, Lange T, Brooks SJ, Schiöth HB, Schultes B, Born J, Oster H, Hallschmid M (2012) Diurnal rhythm of circulating nicotinamide phosphoribosyltransferase (Nampt/Visfatin/PBEF): impact of sleep loss and relation to glucose metabolism. J Clin Endocrinol Metab 97(2):E218–E222
Bergö M, Olivecrona G, Olivecrona T (1996) Diurnal rhythms and effects of fasting and refeeding on rat adipose tissue lipoprotein lipase. Am J Physiol 271:E1092–E1097
Berk ML, Finkelstein JA (1981) An autoradiographic determination of the efferent projections of the suprachiasmatic nucleus of the hypothalamus. Brain Res 226:1–13
Berndt J, Klöting N, Kralisch S, Kovacs P, Fasshauer M, Schön MR, Stumvoll M, Blüher M (2005) Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 54:2911–2916
Bittman EL, Crandell RG, Lehman MN (1989) Influences of the paraventricular and suprachiasmatic nuclei and olfactory bulbs on melatonin responses in the golden hamster. Biol Reprod 40:118–126
Bos NPA, Mirmiran M (1990) Circadian rhythms in spontaneous neuronal discharges of the cultured suprachiasmatic nucleus. Brain Res 511:158–162

Boucher J, Daviaud D, Valet P (2005) Adipokine expression profile in adipocytes of different mouse models of obesity. Horm Metab Res 37:761–767

Bowers CW, Baldwin C, Zigmond RE (1984) Sympathetic reinnervation of the pineal gland after postganglionic nerve lesion does not restore normal pineal function. J Neurosci 4:2010–2015

Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B, Feistner H, Hesch RD, von zur Muhlen A (1990) Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. J Clin Endocrinol Metab 70:403–409

Brown SA, Azzi A (2013) Peripheral circadian oscillators in mammals. In: Kramer A, Merrow M (eds) Circadian clocks, vol 217, Handbook of experimental pharmacology. Springer, Heidelberg

Buhr ED, Takahashi JS (2013) Molecular components of the mammalian circadian clock. In: Kramer A, Merrow M (eds) Circadian clocks, vol 217, Handbook of experimental pharmacology. Springer, Heidelberg

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

Buijs RM, Van Eden CG (2000) The integration of stress by the hypothalamus, amygdale and prefrontal cortex: balance between the autonomic nervous system and the neuroendocrine system. Prog Brain Res 126:117–132

Buijs RM, Hou YX, Shinn S, Renaud LP (1994) Ultrastructural evidence for intra- and extranuclear projections of GABAergic neurons of the suprachiasmatic nucleus. J Comp Neurol 340: 381–391

Buijs RM, Wortel J, Van Heerikhuize JJ, Feenstra MGP, 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 RM, Chun SJ, Niijima A, Romijn HJ, Nagai K (2001) Parasympathetic and sympathetic control of the pancreas: a role for the suprachiasmatic nucleus and other hypothalamic centers that are involved in the regulation of food intake. J Comp Neurol 431:405–423

Buijs RM, la Fleur SE, Wortel J, Van Heijningen C, Zuiddam L, Mettenleiter TC, Kalsbeek A, Nagai K, Niijima A (2003) The suprachiasmatic nucleus balances sympathetic and parasympathetic output to peripheral organs through separate preautonomic neurons. J Comp Neurol 464:36–48

Buijs RM, Scheer FA, Kreier F, Yi CX, Bos N, Goncharuk VD, Kalsbeek A (2006) Organization of circadian functions: interaction with the body. Prog Brain Res 153:341360

Burgess HJ, Trinder J, Kim Y, Luke D (1997) Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol 273:H1761–H1768

Burgueño A, Gemma C, Gianotti TF, Sookoian S, Pirola CJ (2010) Increased levels of resistin in rotating shift workers: a potential mediator of cardiovascular risk associated with circadian misalignment. Atherosclerosis 210:625–629

Cailotto C, van Heijningen C, van der Vliet J, van der Plasse G, Habold C, Kalsbeek A, Pévet P, Buijs RM (2008) Daily rhythms in metabolic liver enzymes and plasma glucose require a balance in the autonomic output to the liver. Endocrinology 149:1914–1925

Cassone VM, Speh JC, Card JP, Moore RY (1988) Comparative anatomy of the mammalian hypothalamic suprachiasmatic nucleus. J Biol Rhythms 3:71–91

Challet E, Pévet P (2003) Interactions between photic and nonphotic stimuli to synchronize the master circadian clock in mammals. Front Biosci 8:S246–S257

Chen MP, Chung FM, Chang DM, Tsai JC, Huang HF, Shin SJ, Lee YJ (2006) Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 91:295–299

Cheng MY, Bullock CM, Li C, Lee AG, Bermak JC, Belluzzi J, Weaver DR, Leslie FM, Zhou QY (2002) Prokineticin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. Nature 417:405–410

Christodoulides C, Lagathu C, Sethi JK, Vidal-Puig A (2009) Adipogenesis and WNT signalling. Trends Endocrinol Metab 20:16–24

Collu R, Du Ruisseau P, Taché Y, Ducharme JR (1977) Thyrotropin-releasing hormone in rat brain: nyctohemeral variations. Endocrinology 100:1391–1393
Cornish S, Cawthorne MA (1978) Fatty acid synthesis in mice during the 24 hr cycle and during meal-feeding. Horm Metab Res 10:286–290
Covarrubias L, Uribe RM, Mendez M, Charli JL, Joseph-Bravo P (1988) Neuronal TRH synthesis: developmental and circadian TRH mRNA levels. Biochem Biophys Res Commun 151: 615–622
Covarrubias L, Redondo JL, Vargas MA, Uribe RM, Mendez M, Joseph-Bravo P, Charli JL (1994) In vitro TRH release from hypothalamus slices varies during the diurnal cycle. Neurochem Res 19:845–850
Csaki A, Kocsis K, Halasz B, Kiss J (2000) Localization of glutamatergic/aspartatergic neurons projecting to the hypothalamic paraventricular nucleus studied by retrograde transport of [3H] D-aspartate autoradiography. Neuroscience 101:637–655
Cuesta M, Clesse D, Pévet P, Challet E (2009) From daily behavior to hormonal and neurotransmitters rhythms: comparison between diurnal and nocturnal rat species. Horm Behav 55:338–347
Cui LN, Coderre E, Renaud LP (2001) Glutamate and GABA mediate suprachiasmatic nucleus inputs to spinal-projecting paraventricular neurons. Am J Physiol 281:R1283–R1289
Dardente H, Menet JS, Challet E, Tournier BB, Pévet P, Masson-Pévet M (2004) Daily and circadian expression of neuropeptides in the suprachiasmatic nuclei of nocturnal and diurnal rodents. Mol Brain Res 124:143–151
De La Iglesia HO, Blaustein JD, Bittman EL (1995) The suprachiasmatic area in the female hamster projects to neurons containing estrogen receptors and GnRH. Neuroreport 6: 1715–1722
De La Iglesia HO, Meyer J, Schwartz WJ (2003) Lateralization of circadian pacemaker output: activation of left- and right-sided luteinizing hormone-releasing hormone neurons involves a neural rather than a humoral pathway. J Neurosci 23:7412–7414
De Vries GJ, Buijs RM, Sluiter AA (1984) Gonadal hormone actions on the morphology of the vasopressinergic innervation of the adult rat brain. Brain Res 298:141–145
Drijfhout WJ, Van Der Linde AG, Kooi SE, Grol CJ, Westerink BH (1996) Norepinephrine release in the rat pineal gland: the input from the biological clock measured by in vivo microdialysis. J Neurochem 66:748–755
Drijfhout WJ, Brons HF, Oakley N, Hagan RM, Grol CJ, Westerink BH (1997) A microdialysis study on pineal melatonin rhythms in rats after an 8-h phase advance: new characteristics of the underlying pacemaker. Neuroscience 80:233–239
Drucker-Colin R, Aguilar-Roblero R, Garcia-Hernandez F, Fernandez-Cancino F, Rattoni FB (1984) Fetal suprachiasmatic nucleus transplants: diurnal rhythm recovery of lesioned rats. Brain Res 311:353–357
Earnest DJ, Sladek CD (1986) Circadian rhythms of vasopressin release from individual rat suprachiasmatic explants in vitro. Brain Res 382:129–133
Elimam A, Marcus C (2002) Meal timing, fasting and glucocorticoids interplay in serum leptin concentrations and diurnal profile. Eur J Endocrinol 147:181–188
Everett JW, Sawyer CH (1950) A 24-hour periodicity in the 'LH release apparatus' of female rats, disclosed by barbiturate sedation. Endocrinology 47:198–218
Fain JN, Cheema PS, Bahouth SW, Hiler ML (2003) Resistin release by human adipose tissue explants in primary culture. Biochem Biophys Res Commun 300:674–678
Farooqi IS (2011) Genetic, molecular and physiological insights into human obesity. Eur J Clin Invest 41:451–455
Flier JS, Maratos-Flier E (2010) Lasker lauds leptin. Cell Metab 12:317–320
Fliers E, Guldenaar SEF, Wiersinga WM, Swaab DF (1997) Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 82:4032–4036

Fliers E, Alkemade A, Wiersinga WM (2001) The hypothalamic-pituitary-thyroid axis in critical illness. Best Pract Res Clin Endocrinol Metab 15:453–464

Forsling ML (1993) Neurohypophysial hormones and circadian rhythm. Ann NY Acad Sci 689: 382–395

Francl JM, Kaur G, Glass JD (2010) Regulation of vasoactive intestinal polypeptide release in the suprachiasmatic nucleus circadian clock. Neuroreport 21:1055–1059

Fukuda H, Greer MA (1975) The effect of basal hypothalamic deafferentation on the nycthemeral rhythm of plasma TSH. Endocrinology 97:749–752

Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaka S, Hiramatsu R, Matsuzawa Y, Shimomura I (2005) Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 307:426–430

Funabashi T, Shinohara K, Mitsushima D, Kimura F (2000a) Estrogen increases arginine-vasopressin V1a receptor mRNA in the preoptic area of young but not of middle-aged female rats. Neurosci Lett 285:205–208

Funabashi T, Shinohara K, Mitsushima D, Kimura F (2000b) Gonadotropin-releasing hormone exhibits circadian rhythm in phase with arginine-vasopressin in co-cultures of the female rat preoptic area and suprachiasmatic nucleus. J Neuroendocrinol 12:521–528

Garaulet M, Ordovás JM, Gómez-Abellán P, Martínez JA, Madrid JA (2011) An approximation to the temporal order in endogenous circadian rhythms of genes implicated in human adipose tissue metabolism. J Cell Physiol 226:2075–2080

Gavrila A, Peng CK, Chan JL, Mietus JE, Goldberger AL, Mantzoros CS (2003) Diurnal and ultradian dynamics of serum adiponectin in healthy men: comparison with leptin, circulating soluble leptin receptor, and cortisol patterns. J Clin Endocrinol Metab 88:2838–2843

Gibson EM, Humber SA, Jain S et al (2008) Alterations in RFamide-related peptide expression are coordinated with the preovulatory luteinizing hormone surge. Endocrinology 149:4958–4969

Gillette MU, Reppert SM (1987) The hypothalamic suprachiasmatic nuclei: circadian patterns of vasopressin secretion and neuronal activity in vitro. Brain Res Bull 19:135–139

Goel N, Lee TM, Smale L (1999) Suprachiasmatic nucleus and intergeniculate leaflet in the diurnal rodent Octodon degus: Retinal projections and immunocytochemical characterization. Neuroscience 92:1491–1509

Goichot B, Weibel L, Chapotot F, Gronfier C, Piquard F, Brandenberger G (1998) Effect of the shift of the sleep-wake cycle on three robust endocrine markers of the circadian clock. Am J Physiol Endocrinol Metab 275:E243–E248

Graham ES, Littlewood P, Turnbull Y, Mercer JG, Morgan PJ, Barrett P (2005) Neuromedin-U is regulated by the circadian clock in the SCN of the mouse. Eur J Neurosci 21:814–819

Greenspan SL, Klibansk A, Schoenfeld D, Ridgeway EC (1986) Pulsatile secretion of thyrotropin in man. J Clin Endocrinol Metab 63:661–668

Günther O, Landgraf R, Schuart J, Unger H (1984) Vasopressin in cerebrospinal fluid (CSF) and plasma of conscious rabbits – circadian variations. Exp Clin Endocrinol Diab 83:367–369

Guo H, Brewer JM, Champhekar A, Harris RB, Bittman EL (2005) Differential control of peripheral circadian rhythms by suprachiasmatic-dependent neural signals. Proc Natl Acad Sci USA 102:3111–3116

Hagström-Toft E, Bolinder J, Ungerstedt U, Arner P (1997) A circadian rhythm in lipid mobilization which is altered in IDDM. Diabetologia 40:1070–1078

Hahm SH, Eiden LE (1998) Five discrete cis-active domains direct cell type-specific transcription of the vasoactive intestinal peptide (VIP) gene. J Biol Chem 273:17086–17094

Halberg N, Wernstedt-Asterholm I, Scherer PE (2008) The adipocyte as an endocrine cell. Endocrinol Metab Clin North Am 37:753–768

Hallschmid M, Randeva H, Tan BK, Kern W, Lehnert H (2009) Relationship between cerebrospinal fluid visfatin (PBEF/Nampt) levels and adiposity in humans. Diabetes 58:637–640

Harper DG, Stopa EG, Kuo-Leblanc V, Mckee AC, Asayama K, Volicer L, Kowall N, Satlin A (2008) Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. Brain 131:1609–1617

Hastings MH, Herbert J (1986) Neurotoxic lesions of the paraventriculo-spinal projection block the nocturnal rise in pineal melatonin synthesis in the syrian hamster. Neurosci Lett 69:1–6

Hayes AL, Xu F, Babineau D, Patel SR (2011) Sleep duration and circulating adipokine levels. Sleep 34:147–152

Hems DA, Rath EA, Verrinder TR (1975) Fatty acid synthesis in liver and adipose tissue of normal and genetically obese (ob/ob) mice during the 24-hour cycle. Biochem J 150:167–173

Hermes MLHJ, Coderre EM, Buijs RM, Renaud LP (1996) GABA and glutamate mediate rapid neurotransmission from suprachiasmatic nucleus to hypothalamic paraventricular nucleus in the rat. J Physiol 496:749–757

Hermes MLHJ, Ruijter JM, Klop A, Buijs RM, Renaud LP (2000) Vasopressin increases GABAergic inhibition of rat hypothalamic paraventricular nucleus neurons in vitro. J Neurophysiol 83:705–711

Herzog ED, Geusz ME, Khalsa SBS, Straume M, Block GD (1997) Circadian rhythms in mouse suprachiasmatic nucleus explants on multi-microelectrode plates. Brain Res 757:285–290

Hilton MF, Umali MU, Czeisler CA, Wyatt JK, Shea SA (2000) Endogenous circadian control of the human autonomic nervous system. Comput Cardiol 27:197–200

Hofman MA, Swaab DF (1994) Alterations in circadian rhythmicity of the vasopressin-producing neurons of the human suprachiasmatic nucleus (SCN) with aging. Brain Res 651:134–142

Hoorneman EMD, Buijs RM (1982) Vasopressin fiber pathways in the rat brain following suprachiasmatic nucleus lesioning. Brain Res 243:235–241

Houghton SG, Zarroug AE, Duenes JA, Fernandez-Zapico ME, Sarr MG (2006) The diurnal periodicity of hexose transporter mRNA and protein levels in the rat jejunum: role of vagal innervation. Surgery 139:542–549

Inouye SIT, Kawamura H (1979) Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. Proc Natl Acad Sci USA 76:5962–5966

Ishida A, Mutoh T, Ueyama T et al (2005) Light activates the adrenal gland: timing of gene expression and glucocorticoid release. Cell Metab 2:297–307

Jasper MS, Engeland WC (1994) Splanchnic neural activity modulates ultradian and circadian rhythms in adrenocortical secretion in awake rats. Neuroendocrinology 59:97–109

Jin XW, Shearman LP, Weaver DR, Zylka MJ, De Vries GJ, Reppert SM (1999) A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. Cell 96: 57–68

Johnson RF, Smale L, Moore RY, Morin LP (1989) Paraventricular nucleus efferents mediating photoperiodism in male golden hamsters. Neurosci Lett 98:85–90

Jolkonen J, Tuomisto L, Van Wimersma Greidanus TB, Riekkinen PJ (1988) Vasopressin levels in the cerebrospinal fluid of rats with lesions of the paraventricular and suprachiasmatic nuclei. Neurosci Lett 86:184–188

Jordan D, Rousset B, Perrin F, Fournier M, Orgiazzi J (1980) Evidence for circadian variations in serum thyrotropin, 3,5,3′-triiodothyronine, and thyroxine in the rat. Endocrinology 107: 1245–1248

Kalsbeek A, Buijs RM (2002) Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting. Cell Tissue Res 309: 109–118

Kalsbeek A, Strubbe JH (1998) Circadian control of insulin secretion is independent of the temporal distribution of feeding. Physiol Behav 63:553–560

Kalsbeek A, Buijs RM, Van Heerikhuize JJ, Arts M, Van Der Woude TP (1992) Vasopressin-containing neurons of the suprachiasmatic nuclei inhibit corticosterone release. Brain Res 580: 62–67

Kalsbeek A, Teclemariam-Mesbah R, Pévet P (1993a) Efferent projections of the suprachiasmatic nucleus in the golden hamster (Mesocricetus auratus). J Comp Neurol 332:293–314

Kalsbeek A, Rikkers M, Vivien-Roels B, Pévet P (1993b) Vasopressin and vasoactive intestinal peptide infused in the paraventricular nucleus of the hypothalamus elevate plasma melatonin levels. J Pineal Res 15:46–52

Kalsbeek A, Buijs RM, Engelmann M, Wotjak CT, Landgraf R (1995) In vivo measurement of a diurnal variation in vasopressin release in the rat suprachiasmatic nucleus. Brain Res 682: 75–82

Kalsbeek A, Drijfhout WJ, Westerink BHC, Van Heerikhuize JJ, Van Der Woude T, Van Der Vliet J, Buijs RM (1996a) GABA receptors in the region of the dorsomedial hypothalamus of rats are implicated in the control of melatonin. Neuroendocrinology 63:69–78

Kalsbeek A, Van Der Vliet J, Buijs RM (1996b) Decrease of endogenous vasopressin release necessary for expression of the circadian rise in plasma corticosterone: a reverse microdialysis study. J Neuroendocrinol 8:299–307

Kalsbeek A, Van Heerikhuize JJ, Wortel J, Buijs RM (1996c) 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, Cutrera RA, Van Heerikhuize JJ, Van Der Vliet J, Buijs RM (1999) GABA release from SCN terminals is necessary for the light-induced inhibition of nocturnal melatonin release in the rat. Neuroscience 91:453–461

Kalsbeek A, Barassin S, van Heerikhuize JJ, van der Vliet J, Buijs RM (2000a) Restricted daytime feeding attenuates reentrainment of the circadian melatonin rhythm after an 8-h phase advance of the light–dark cycle. J Biol Rhythms 15:57–66

Kalsbeek A, Fliers E, Franke AN, Wortel J, Buijs RM (2000b) Functional connections between the suprachiasmatic nucleus and the thyroid gland as revealed by lesioning and viral tracing techniques in the rat. Endocrinology 141:3832–3841

Kalsbeek A, Garidou ML, Palm IF, Van Der Vliet J, Simonneaux V, Pévet P, Buijs RM (2000c) Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. Eur J Neurosci 12:3146–3154

Kalsbeek A, Fliers E, Romijn JA, La Fleur SE, Wortel J, Bakker O, Endert E, Buijs RM (2001) The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. Endocrinology 142:2677–2685

Kalsbeek A, La Fleur SE, Van Heijningen C, Buijs RM (2004) Suprachiasmatic GABAergic inputs to the paraventricular nucleus control plasma glucose concentrations in the rat via sympathetic innervation of the liver. J Neurosci 24:7604–7613

Kalsbeek A, Buijs RM, van Schaik R, Kaptein E, Visser TJ, Doulabi BZ, Fliers E (2005) Daily variations in type II iodothyronine deiodinase activity in the rat brain as controlled by the biological clock. Endocrinology 146:1418–1427

Kalsbeek A, Palm IF, La Fleur SE, Scheer FAJL, Perreau-Lenz S, Ruiter M, Kreier F, Cailotto C, Buijs RM (2006) SCN outputs and the hypothalamic balance of life. J Biol Rhythms 21: 458–469

Kalsbeek A, Foppen E, Schalij I, Van Heijningen C, van der Vliet J, Fliers E, Buijs RM (2008a) Circadian control of the daily plasma glucose rhythm: an interplay of GABA and glutamate. PLoS One 3:e3194

Kalsbeek A, Verhagen LA, Schalij I, Foppen E, Saboureau M, Bothorel B, Buijs RM, Pévet P (2008b) Opposite actions of hypothalamic vasopressin on circadian corticosterone rhythm in nocturnal versus diurnal species. Eur J Neurosci 27:818–827

Kalsbeek A, Scheer FA, Perreau-Lenz S, La Fleur SE, Yi CX, Fliers E, Buijs RM (2011) Circadian disruption and SCN control of energy metabolism. FEBS Lett 585:1412–1426

Kappers JA (1960) The development, topographical relations and innervation of the epiphysis cerebri in the albino rat. Z Zellforsch 52:163–215

Kennaway DJ, Owens JA, Voultsios A, Wight N (2011) Adipokines and adipocyte function in clock mutant mice that retain melatonin rhythmicity. Obesity 15:1–11

Khan AR, Kauffman AS (2011) The role of kisspeptin and RFRP-3 neurons in the circadian-timed preovulatory luteinizing hormone surge. J Neuroendocrinol 24:131–143

Kita Y, Shiozawa M, Jin WH, Majewski RR, Besharse JC, Greene AS, Jacob HJ (2002) Implications of circadian gene expression in kidney, liver and the effects of fasting on pharmacogenomic studies. Pharmacogenetics 12:55–65

Klein DC, Moore RY (1979) Pineal N-acetyltransferase and hydroxyindole-o-methyl-transferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. Brain Res 174: 245–262

Klein DC, Weller JL, Moore RY (1971) Melatonin metabolism: neural regulation of pineal serotonin: acetyl coenzyme A N-acetyltransferase activity. Proc Natl Acad Sci USA 68: 3107–3110

Klein DC, Smoot R, Weller JL et al (1983) Lesions of the paraventricular nucleus area of the hypothalamus disrupt the suprachiasmatic-spinal cord circuit in the melatonin rhythm generating system. Brain Res Bull 10:647–652

Kneisley LW, Moskowitz MA, Lynch HG (1978) Cervical spinal cord lesions disrupt the rhythm in human melatonin excretion. J Neural Transm Suppl 13:311–323

Kraves S, Weitz CJ (2006) A role for cardiotrophin-like cytokine in the circadian control of mammalian locomotor activity. Nat Neurosci 9:212–219

Kreier F (2005) Dual sympathetic and parasympathetic hypothalamic output to white adipose tissue. In: Autonomic nervous control of white adipose tissue, Chap 4. Dissertation. University of Amsterdam, Amsterdam

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

Kreier F, Kap YS, Mettenleiter T, Van Heijningen C, Van Der Vliet J, Kalsbeek A, Sauerwein H, Fliers E, Romijn JA, Buijs RM (2006) Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in Type2 diabetes. Endocrinology 147:1140–1147

La Fleur SE (2003) Daily rhythms in glucose metabolism: suprachiasmatic nucleus output to peripheral tissue. J Neuroendocrinol 15:315–322

La Fleur SE, Kalsbeek A, Wortel J, Buijs RM (2000) Polysynaptic neural pathways between the hypothalamus, including the suprachiasmatic nucleus, and the liver. Brain Res 871:50–56

Larsen PJ, Enquist LW, Card JP (1998) Characterization of the multisynaptic neuronal control of the rat pineal gland using viral transneuronal tracing. Eur J Neurosci 10:128–145

Lee JW, Erskine MS (2000) Pseudorabies virus tracing of neural pathways between the uterine cervix and CNS: effects of survival time, estrogen treatment, rhizotomy, and pelvic nerve transection. J Comp Neurol 418:484–503

Lehman MN, Bittman EL, Newman SW (1984) Role of the hypothalamic paraventricular nucleus in neuroendocrine responses to daylength in the golden hamster. Brain Res 308:25–32

Lehman MN, Silver R, Gladstone WR, Kahn RM, Gibson M, Bittman EL (1987) Circadian rhythmicity restored by neural transplant. Immunocytochemical characterization of the graft and its integration with the host brain. J Neurosci 7:1626–1638

Lerner ABT, Lee TH, Mori W (1958) Isolation of melatonin, the pineal gland factor that lightens melanocytes. J Am Chem Soc 80:2587

Lilley TR, Wotus C, Taylor D, Lee JM, de la Iglesia HO (2012) Circadian regulation of cortisol release in behaviorally split golden hamsters. Endocrinology 153(2):732–738

Liu RH, Mizuta M, Matsukura S (2004) The expression and functional role of nicotinic acetylcholine receptors in rat adipocytes. J Pharmacol Exp Ther 310:52–58

Loh DH, Abad C, Colwell CS, Waschek JA (2008) Vasoactive intestinal peptide is critical for circadian regulation of glucocorticoids. Neuroendocrinology 88:246–255

Lynch HJ (1971) Diurnal oscillations in pineal melatonin content. Life Sci 10:791–795

Martino E, Bambini G, Vaudaga G, Breccia M, Baschieri L (1985) Effects of continuous light and dark exposure on hypothalamic thyrotropin-releasing hormone in rats. J Endocrinol Invest 8: 31–33

Maury E, Brichard SM (2010) Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol 314:1–16
Messager S (2005) Kisspeptin and its receptor: new gatekeepers of puberty. J Neuroendocrinol 17:687–688
Meyer-Bernstein EL, Jetton AE, Matsumoto SI, Markuns JF, Lehman MN, Bittman EL (1999) Effects of suprachiasmatic transplants on circadian rhythms of neuroendocrine function in golden hamsters. Endocrinology 140:207–218
Mikkelsen JD, Simonneaux V (2009) The neuroanatomy of the kisspeptin system in the mammalian brain. Peptides 30:26–33
Miller BH, Olson SL, Levine JE, Turek FW, Horton TH, Takahashi JS (2006) Vasopressin regulation of the proestrous luteinizing hormone surge in wild-type and clock mutant mice. Biol Reprod 75:778–784
Moore RY (1978) Neural control of pineal function in mammals and birds. J Neural Transm Suppl 13:47–58
Moore RM (1996a) Entrainment pathways and the functional organization of the circadian system. Prog Brain Res 111:103–119
Moore RY (1996b) Neural control of the pineal gland. Behav Brain Res 73:125–130
Moore RY, Klein DC (1974) Visual pathways and the central neural control of a circadian rhythm in pineal serotonin N-acetyltransferase activity. Brain Res 71:17–33
Moore RY, Speh JC (1993) GABA Is the principal neurotransmitter of the circadian system. Neurosci Lett 150:112–116
Morin LP, Shivers KY, Blanchard JH, Muscat L (2006) Complex organization of mouse and rat suprachiasmatic nucleus. Neuroscience 137:1285–1297
Nakamura W, Honma S, Shirakawa T, Honma K (2001) Regional pacemakers composed of multiple oscillator neurons in the rat suprachiasmatic nucleus. Eur J Neurosci 14:666–674
Nonogaki K (2000) New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia 43:533–549
Nunez AA, Brown MH, Youngstrom TG (1985) Hypothalamic circuits involved in the regulation of seasonal and circadian rhythms in male golden hamsters. Brain Res Bull 15:149–153
Oishi K, Miyazaki K, Kadota K, Kikuno R, Nagase T, Atsumi G, Ohkura N, Azama T, Mesaki M, Yukimasa S, Kobayashi H, Iitaka C, Umehara T, Horikoshi M, Kudo T, Shimizu Y, Yano M, Monden M, Machida K, Matsuda J, Horie S, Todo T, Ishida N (2002) Genome-wide expression analysis of mouse liver reveals CLOCK-regulated circadian output genes. J Biol Chem 278: 41519–41527
Okamura H, Berod A, Julien JF, Geffard M, Kitahama K, Mallet J, Bobillier P (1989) Demonstration of GABAergic cell bodies in the suprachiasmatic nucleus: in situ hybridization of glutamic acid decarboxylase (GAD) mRNA and immunocytochemistry of GAD and GABA. Neurosci Lett 102:131–136
Olcese J, Reuss S, Steinlechner S (1987) Electrical stimulation of the hypothalamic nucleus paraventricularis mimics the effects of light on pineal melatonin synthesis. Life Sci 40: 455–459
Oliver P, Ribot J, Rodríguez AM, Sánchez J, Picó C, Palou A (2006) Resistin as a putative modulator of insulin action in the daily feeding/fasting rhythm. Eur J Physiol 452:260–267
Oster H, Damerow S, Kiessling S et al (2006) The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. Cell Metab 4:163–173
Ostrowski NL, Lolait SJ, Young WS (1994) Cellular localization of vasopressin V1a receptor messenger ribonucleic acid in adult male rat brain, pineal, and brain vasculature. Endocrinology 135:1511–1528
Ottenweller JE, Hedge GA (1982) Diurnal variations of plasma thyrotropin, thyroxine, and triiodothyronine in female rats are phase shifted after inversion of the photoperiod. Endocrinology 111:509–514
Otway DT, Frost G, Johnston JD (2009) Circadian rhythmicity in murine pre-adipocyte and adipocyte cells. Chronobiol Int 26:1340–1354

Palm IF, Van Der Beek EM, Wiegant VM, Buijs RM, Kalsbeek A (1999) Vasopressin induces an LH surge in ovariectomized, estradiol-treated rats with lesion of the suprachiasmatic nucleus. Neuroscience 93:659–666

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

Parker DC, Pekary AE, Hershman JM (1976) Effect of normal and reversed sleep-wake cycles upon nyctohemeral rhythmicity of plasma thyrotropin: evidence suggestive of an inhibitory influence in sleep. J Clin Endocrinol Metab 43:318–329

Perreau-Lenz S, Kalsbeek A, Garidou ML, Wortel J, Van Der Vliet J, Van Heijningen C, Simonneaux V, Pévet P, Buijs RM (2003) Suprachiasmatic control of melatonin synthesis in rats: inhibitory and stimulatory mechanisms. Eur J Neurosci 17:221–228

Perreau-Lenz S, Kalsbeek A, Pévet P, Buijs RM (2004) Glutamatergic clock output stimulates melatonin synthesis at night. Eur J Neurosci 19:318–324

Pickard GE, Turek FW (1983) The hypothalamic paraventricular nucleus mediates the photoperiodic control of reproduction but not the effects of light on the circadian rhythm of activity. Neurosci Lett 43:67–72

Pickard GE, Kahn R, Silver R (1984) Splitting of the circadian rhythm of body temperature in the golden hamster. Physiol Behav 32:763–766

Pittendrigh CS, Daan S (1976) A functional analysis of circadian pacemakers in nocturnal rodents. V. Pacemaker structure: a clock for all seasons. J Comp Physiol A 106:333–355

Poulos SP, Hausman DB, Hausman GJ (2010) The development and endocrine functions of adipose tissue. Mol Cell Endocrinol 323:20–34

Prosser RA, Bergeron HE (2003) Leptin phase-advances the rat suprachiasmatic circadian clock in vitro. Neurosci Lett 336:139–142

Ptitsyn AA, Zvonic S, Conrad SA, Scott LK, Mynatt RL, Gimble JM (2006) Circadian clocks are resounding in peripheral tissues. PLoS Comp Biol 2:e16

Puschel GP (2004) Control of hepatocyte metabolism by sympathetic and parasympathetic hepatic nerves. Anat Rec 280A:854

Rajala MW, Qi Y, Patel HR, Takahashi N, Banerjee R, Pajvani UB, Sinha MK, Gingerich RL, Scherer PE, Ahima RS (2004) Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. Diabetes 53:1671–1679

Ralph CL, Mull D, Lynch HJ, Hedlund L (1971) A melatonin rhythm persists in rat pineals in darkness. Endocrinology 89:1361–1366

Ralph MR, Foster RG, Davis FC, Menaker M (1990) Transplanted suprachiasmatic nucleus determines circadian period. Science 247:975–978

Ramsey KM, Yoshino J, Brace CS, Abrassart D, Kobayashi Y, Marcheva B, Hong HK, Chong JL, Buhr ED, Lee C, Takahashi JS, Imai S, Bass J (2009) Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. Science 324:651–654

Reiter RJ, King TS, Richardson BA, Hurlbut EC (1982) Studies on pineal melatonin levels in a diurnal species, the eastern chipmunk (Tamias striatus): effects of light at night, propranolol administration or superior cervical ganglionectomy. J Neural Transm 54:275–284

Reppert SM, Artman HG, Swaminathan S, Fisher DA (1981) Vasopressin exhibits a rhythmic daily pattern in cerebrospinal fluid but not in blood. Science 213:1256–1257

Reppert SM, Schwartz WJ, Uhl GR (1987) Arginine vasopressin: a novel peptide rhythm in cerebrospinal fluid. Trends Neurosci 10:76–80

Reuss S, Olcese J, Vollrath L (1985) Electrical stimulation of the hypothalamic paraventricular nuclei inhibits pineal melatonin synthesis in male rats. Neuroendocrinology 41:192–196

Reuss S, Hurlbut EC, Speh JC, Moore RY (1989) Immunohistochemical evidence for the presence of neuropeptides in the hypothalamic suprachiasmatic nucleus of ground squirrels. Anat Rec 225:341–346

Reuss S, Stehle J, Schröder H, Vollrath L (1990) The role of the hypothalamic paraventricular nuclei for the regulation of pineal melatonin synthesis: new aspects derived from the vasopressin-deficient Brattleboro rat. Neurosci Lett 109:196–200

Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ (2008) Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA 299:2642–2655

Robinson ICAF, Coombes JE (1993) Neurohypophysial peptides in cerebrospinal fluid: an update. Ann NY Acad Sci 689:269–283

Robinson BG, Frim DM, Schwartz WJ, Majzoub JA (1988) Vasopressin mRNA in the suprachiasmatic nuclei: daily regulation of polyadenylate tail length. Science 241:342–344

Roelfsema F, Pereira AM, Veldhuis JD, Adriaanse R, Endert E, Fliers E, Romijn JA (2009) Thyrotropin secretion profiles are not different in men and women. J Clin Endocrinol Metab 94:3964–3967

Roelfsema F, Pereira AM, Adriaanse R, Endert E, Fliers E, Romijn JA, Veldhuis JD (2010) Thyrotropin secretion in mild and severe primary hypothyroidism is distinguished by amplified burst mass and basal secretion with increased spikiness and approximate entropy. J Clin Endocrinol Metab 95:928–934

Roenneberg T, Kantermann T, Juda M, Vetter C, Allebrandt KV (2013) Light and the human circadian clock. In: Kramer A, Merrow M (eds) Circadian clocks, vol 217, Handbook of experimental pharmacology. Springer, Heidelberg

Romijn JA, Wiersinga WM (1990) Decreased nocturnal surge of thyrotropin in nonthyroidal illness. J Clin Endocrinol Metab 70:35–42

Romijn JA, Adriaanse R, Brabant G, Prank K, Endert E, Wiersinga WM (1990) Pulsatile secretion of thyrotropin during fasting: a decrease of thyrotropin pulse amplitude. J Clin Endocrinol Metab 70:1631–1636

Rookh HV, Azukizawa M, DiStefano JJ III, Ogihara T, Hershman JM (1979) Pituitary-thyroid hormone periodicities in serially sampled plasma of unanesthetized rats. Endocrinology 104:851–856

Saeb-Parsy K, Dyball REJ (2003) Defined cell groups in the rat suprachiasmatic nucleus have different day/night rhythms of single-unit activity in vivo. J Biol Rhythms 18:26–42

Schaap J, Albus H, VanderLeest HT, Eilers PH, Detari L, Meijer JH (2003) Heterogeneity of rhythmic suprachiasmatic nucleus neurons: implications for circadian waveform and photoperiodic encoding. Proc Natl Acad Sci USA 100:15994–15999

Scheer FA, Ter Horst GJ, van Der Vliet J, Buijs RM (2001) Physiological and anatomic evidence for regulation of the heart by suprachiasmatic nucleus in rats. Am J Physiol 280:H1391–H1399

Scheer FA, Van Doornen LJ, Buijs RM (2004a) Light and diurnal cycle affect autonomic cardiac balance in human; possible role for the biological clock. Auton Neurosci 110:44–48

Scheer FA, Van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM (2004b) Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertension 43:192–197

Scheer FA, Zeitzer JM, Ayas NT, Brown R, Czeisler CA, Shea SA (2006) Reduced sleep efficiency in cervical spinal cord injury; association with abolished night time melatonin secretion. Spinal Cord 44:78–81

Scheer FA, Hilton MF, Mantzoros CS, Shea SA (2009) Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci USA 106:4453–4458

Scheer FAJL, Chan JL, Fargnoli J, Chamberland J, Arampatzi K, Shea SA, Blackburn GL, Mantzoros CS (2010) Day/night variations of high-molecular-weight adiponectin and lipocalin-2 in healthy men studied under fed and fasted conditions. Diabetologia 53:2401–2405

Schröder H, Reuss S, Stehle J, Vollrath L (1988a) Intra-arterially administered vasopressin inhibits nocturnal pineal melatonin synthesis in the rat. Comp Biochem Physiol 4:651–653

Schröder H, Stehle J, Henschel M (1988b) Twenty-four hour pineal melatonin synthesis in the vasopressin-deficient Brattleboro rat. Brain Res 459:328–332

Schröder H, Stehle J, Moller M (1989) Stimulation of serotonin-N-acetyltransferase activity in the pineal gland of the mongolian gerbil (Meriones unguiculatus) by intracerebroventricular injection of vasoactive intestinal polypeptide. J Pineal Res 7:393–399
Schwartz WJ, Gainer H (1977) Suprachiasmatic nucleus: use of 14C-labeled deoxyglucose uptake as a functional marker. Science 197:1089–1091
Schwartz DR, Lazar MA (2011) Human resistin: found in translation from mouse to man. Trends Endocrinol Metab 22:259–265
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
Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 406:661–671
Seckl JR, Lightman SL (1987) Diurnal rhythm of vasopressin but not of oxytocin in the cerebrospinal fluid of the goat: lack of association with plasma cortisol rhythm. J Endocrinol 114:477–482
Shea SA, Hilton MF, Orlova C, Ayers RT, Mantzoros CS (2005) Independent circadian and sleep/wake regulation of adipokines and glucose in humans. J Clin Endocrinol Metab 90:2537–2544
Shibata S, Oomura Y, Kita H, Hattori K (1982) Circadian rhythmic changes of neuronal activity in the suprachiasmatic nucleus of the rat hypothalamic slice. Brain Res 247:154–158
Shimazu T (1987) Neuronal regulation of hepatic glucose metabolism in mammals. Diabetes Metab Rev 3:185–206
Shirasaka T, Nakazato M, Matsukura S, Takasaki M, Kannan H (1999) Sympathetic and cardiovascular actions of orexins in conscious rats. Am J Physiol 277:R1780–R1785
Shiuchi T, Haque MS, Okamoto S, Inoue T, Kageyama H, Lee S, Toda C, Suzuki A, Bachman ES, Kim YB, Sakurai T, Yanagisawa M, Shioda S, Imoto K, Minokoshi Y (2009) Hypothalamic orexin stimulates feeding-associated glucose utilization in skeletal muscle via sympathetic nervous system. Cell Metab 10:466–480
Silver R, Lesauter J, Tresco PA, Lehman M (1996) A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. Nature 382: 810–813
Simon C, Gronfier C, Schlienger JL, Brandenberger G (1998) Circadian and ultradian variations of leptin in normal man under continuous enteral nutrition: relationship to sleep and body temperature. J Clin Endocrinol Metab 83:1893–1899
Smale L, Boverhof J (1999) The suprachiasmatic nucleus and intergeniculate leaflet of Arvicanthis niloticus, a diurnal murid rodent from east Africa. J Comp Neurol 403:190–208
Smale L, Cassone VM, Moore RY, Morin LP (1989) Paraventricular nucleus projections mediating pineal melatonin and gonadal responses to photoperiod in the hamster. Brain Res Bull 22:263–269
Södersten P, Henning M, Melin P, Ludin S (1983) Vasopressin alters female sexual behaviour by acting on the brain independently of alterations in blood pressure. Nature 301:608–610
Södersten P, De Vries GJ, Buijs RM, Melin P (1985) A daily rhythm in behavioral vasopressin sensitivity and brain vasopressin concentrations. Neurosci Lett 58:37–41
Södersten P, Boer GJ, De Vries GJ, Buijs RM, Melin P (1986) Effects of vasopressin on female sexual behavior in male rat. Neurosci Lett 69:188–191
Sofroniew MV, Weindl A (1980) Identification of parvocellular vasopressin and neurophysin neurons in the suprachiasmatic nucleus of a variety of mammals including primates. J Comp Neurol 193:659–675
Stark RI, Daniel SS (1989) Circadian rhythm of vasopressin levels in cerebrospinal fluid of the fetus: effect of continuous light. Endocrinology 124:3095–3101
Stehle J, Reuss S, Riemann R, Seidel A, Vollrath L (1991) The role of arginine-vasopressin for pineal melatonin synthesis in the rat: involvement of vasopressinergic receptors. Neurosci Lett 123:131–134
Stephan FK, Berkley KJ, Moss RL (1981) Efferent connections of the rat suprachiasmatic nucleus. Neuroscience 6:2625–2641

Stopa EG, King JC, Lydic R, Schoene WC (1984) Human brain contains vasopressin and vasoactive intestinal polypeptide neuronal subpopulations in the suprachiasmatic region. Brain Res 297:159–163

Strubbe JH, Alingh Prins AJ, Bruggink J, Steffens AB (1987) Daily variation of food-induced changes in blood glucose and insulin in the rat and the control by the suprachiasmatic nucleus and the vagus nerve. J Auton Nerv Syst 20:113–119

Stryjecki C, Mutch DM (2011) Fatty acid-gene interactions, adipokines and obesity. Eur J Clin Nutr 65:285–297

Sun X, Rusak B, Semba K (2000) Electrophysiology and pharmacology of projections from the suprachiasmatic nucleus to the ventromedial preoptic area in rat. Neuroscience 98:715–728

Sun X, Whitefield S, Rusak B, Semba K (2001) Electrophysiological analysis of suprachiasmatic nucleus projections to the ventrolateral preoptic area in the rat. Eur J Neurosci 14:1257–1274

Swaab DF, Pool CW, Nijveldt F (1975) Immunofluorescence of vasopressin and oxytocin in the rat hypothalamo-neurohypophyseal system. J Neural Transm 36:195–215

Swaab DF, Fliers E, Partiman TS (1985) The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Res 342:37–44

Swann JM, Turek FW (1985) Multiple circadian oscillator regulate the timing of behavioral and endocrine rhythms in female golden hamsters. Science 228:898–900

Swanson LW, Cowan WM (1975) The efferent connections of the suprachiasmatic nucleus of the hypothalamus. J Comp Neurol 160:1–12

Swanson LW, Kuypers HGJM (1980) The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. J Comp Neurol 194:555–570

Takahashi JS, Hong HK, Ko CH, McDearmon EL (2008) The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Genet 9:764–775

Teclemariam-Mesbah R, Kalsbeek A, Pévet P, Buijs RM (1997) Direct vasoactive intestinal polypeptide-containing projection from the suprachiasmatic nucleus to spinal projecting hypothalamic paraventricular neurons. Brain Res 748:71–76

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

Tessonneaud A, Locatelli A, Caldani M, Viguier-Martinez MC (1995) Bilateral lesions of the suprachiasmatic nuclei alter the nocturnal melatonin secretion in sheep. J Neuroendocrinol 7: 145–152

Tousson E, Meissl H (2004) Suprachiasmatic nuclei grafts restore the circadian rhythm in the paraventricular nucleus of the hypothalamus. J Neurosci 24:2983–2988

Trujillo ME, Scherer PE (2006) Adipose tissue-derived factors: impact on health and disease. Endocr Rev 27:762–778

Turer AT, Khera A, Ayers CR, Turer CB, Grundy SM, Vega GL, Scherer PE (2011) Adipose tissue mass and location affect circulating adiponectin levels. Diabetologia 54:2515–2524

Uhl GR, Reppert SM (1986) Suprachiasmatic nucleus vasopressin messenger RNA: circadian variation in normal and Brattleboro rats. Science 232:390–393

Van den Berghe G, De Zegher F, Veldhuis JD, Wouters P, Gouwy S, Stockman W, Weekers F, Schetz M, Lauwers P, Bouillon R, Bowers CY (1997) Thyrotrophin and prolactin release in prolonged critical illness: dynamics of spontaneous secretion and effects of growth hormone-secretagogues. Clin Endocrinol 47:599–612

Van den Berghe G, De Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M, Verwaest C, Van Der Vorst E, Lauwers P, Bouillon R, Bowers CY (1998) Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. J Clin Endocrinol Metab 83:309–319

Van Den Pol AN (1991) Glutamate and aspartate immunoreactivity in hypothalamic presynaptic axons. J Neurosci 11:2087–2101

Van Den Pol AN, Gorcs T (1986) Synaptic relationships between neurons containing vasopressin, gastrin-releasing peptide, vasoactive intestinal polypeptide, and glutamate decarboxylase immunoreactivity in the suprachiasmatic nucleus: dual ultrastructural immunocytochemistry with gold-substituted silver peroxidase. J Comp Neurol 252:507–521

Van den Top M, Nolan MF, Lee K, Richardson PJ, Buijs RM, Davies C, Spanswick D (2003) Orexins induce increased excitability and synchronisation of rat sympathetic preganglionic neurones. J Physiol 549:809–821

Van Der Beek EM (1996) Circadian control of reproduction in the female rat. In: Buijs RM, Kalsbeek A, Romijn HJ, Pennartz CMA, Mirmiran M (eds) Progress in brain research, vol 111, Hypothalamic integration of circadian rhythms. Elsevier Science BV, Amsterdam, pp 295–320

Van Der Beek EM, Wiegant VM, Van Der Donk HA, Van Den Hurk R, Buijs RM (1993) Lesions of the suprachiasmatic nucleus indicate the presence of a direct vasoactive intestinal polypeptide-containing projection to gonadotrophin-releasing hormone neurons in the female rat. J Neuroendocrinol 5:137–144

Van Der Beek EM, Van Oudheusen HJC, Buijs RM, Van Der Donk HA, Van Den Hurk 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

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

Vandesande F, Dierickx K, De Mey J (1974) Identification of the vasopressin-neurophysin producing neurons of the rat suprachiasmatic nuclei. Cell Tissue Res 156:377–380

Vida B, Deli L, Hrabovszky E et al (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

Vrang N, Larsen PJ, Mikkelsen JD (1995) Direct projection from the suprachiasmatic nucleus to hypophysiotrophic corticotropin-releasing factor immunoreactive cells in the paraventricular nucleus of the hypothalamus demonstrated by means of Phaseolus vulgaris-leucoagglutinin tract tracing. Brain Res 684:61–69

Vrang N, Mikkelsen JD, Larsen PJ (1997) Direct link from the suprachiasmatic nucleus to hypothalamic neurons projecting to the spinal cord: a combined tracing study using cholera toxin subunit B and Phaseolus vulgaris-leucoagglutinin. Brain Res Bull 44:671–680

Wang P, Mariman E, Renes J, Keijer J (2008) The secretory function of adipocytes in the physiology of white adipose tissue. J Cell Physiol 216:3–13

Watson RE, Langub MC, Engle MG, Maley BE (1995) Estrogen-receptive neurons in the anteroventral periventricular nucleus are synaptic targets of the suprachiasmatic nucleus and peri-suprachiasmatic region. Brain Res 689:254–264

Watts AG (2005) Glucocorticoid regulation of peptide genes in neuroendocrine CRH neurons: a complexity beyond negative feedback. Front Neuroendocrinol 26:109–130

Watts AG, Swanson LW (1987) Efferent projections of the suprachiasmatic nucleus: II. Studies using retrograde transport of fluorescent dyes and simultaneous peptide immunohistochemistry in the rat. J Comp Neurol 258:230–252

Weaver DR (1998) The suprachiasmatic nucleus: a 25-year retrospective. J Biol Rhythms 13: 100–112

Weiss B, Maickel RP (1968) Sympathetic nervous control of adipose tissue lipolysis. Int J Neuropharmacol 7:395–403

Williams WP 3rd, Jarjisian SG, Mikkelsen JD, Kriegsfeld LJ (2011) Circadian control of kisspeptin and a gated GnRH response mediate the preovulatory luteinizing hormone surge. Endocrinology 152:595–606

Wurtman RJ, Axelrod J, Sedvall G, Moore RY (1967) Photic and neural control of the 24-hour norepinephrine rhythm in the rat pineal gland. J Pharmacol Exp Ther 157:487–492

Yang T, Chang C, Tsao C, Hsu Y, Hsu C, Cheng J (2009) Activation of muscarinic M-3 receptor may decrease glucose uptake and lipolysis in adipose tissue of rats. Neurosci Lett 451:57–59

Yanovski J, Witcher J, Adler NT, Markey SP, Klein DC (1987) Stimulation of the paraventricular nucleus area of the hypothalamus elevates urinary 6-hydroxymelatonin during daytime. Brain Res Bull 19:129–133

Yi CX, Serlie MJ, Ackermans MT, Foppen E, Buijs RM, Sauerwein HP, Fliers E, Kalsbeek A (2009) A major role for perifornical orexin neurons in the control of glucose metabolism in rats. Diabetes 58:1998–2005

Yuwiler A (1983) Vasoactive intestinal peptide stimulation of pineal serotonin-N-acetyltransferase activity: general characteristics. J Neurochem 41:146–153

Zeitzer JM, Ayas NT, Shea SA, Brown R, Czeisler CA (2000) Absence of detectable melatonin and preservation of cortisol and thyrotropin rhythms in tetraplegia. J Clin Endocrinol Metab 85:2189–2196

Zeitzer JM, Buckmaster CL, Parker KJ, Hauck CM, Lyons DM, Mignot E (2003) Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. J Neurosci 23:3555–3560

Zhang S, Zeitzer JM, Yoshida Y, Wisor JP, Nishino S, Edgar DM, Mignot E (2004) Lesions of the suprachiasmatic nucleus eliminate the daily rhythm of hypocretin-1 release. Sleep 27:619–627

Zhang W, Zhang N, Sakurai T, Kuwaki T (2009) Orexin neurons in the hypothalamus mediate cardiorespiratory responses induced by disinhibition of the amygdala and bed nucleus of the stria terminalis. Brain Res 1262:25–37