Interactions between endocrine and circadian systems

Anthony H Tsang[1,2], Johanna L Barclay[1,3] and Henrik Oster[1,2]

[1]Circadian Rhythms Group, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany
[2]Chronophysiology Group, Medical Department I, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany
[3]School of Medicine, University of Queensland, Brisbane, Queensland, Australia

Correspondence should be addressed to H Oster
Email
henrik.oster@uksh.de

Abstract

In most species, endogenous circadian clocks regulate 24-h rhythms of behavior and physiology. Clock disruption has been associated with decreased cognitive performance and increased propensity to develop obesity, diabetes, and cancer. Many hormonal factors show robust diurnal secretion rhythms, some of which are involved in mediating clock output from the brain to peripheral tissues. In this review, we describe the mechanisms of clock–hormone interaction in mammals, the contribution of different tissue oscillators to hormonal regulation, and how changes in circadian timing impinge on endocrine signalling and downstream processes. We further summarize recent findings suggesting that hormonal signals may feed back on circadian regulation and how this crosstalk interferes with physiological and metabolic homeostasis.

Key Words
- circadian clocks
- cortisol
- endocrine rhythm
- melatonin
- adipokines

Journal of Molecular Endocrinology
(2014) **52**, R1–R16

Journal of Molecular Endocrinology

Introduction

We live in an environment shaped by various geophysical rhythms. Arguably, one of the most prominent of these rhythms is the succession of day and night. The profound environmental changes brought about by the rotation of the Earth around its axis have promoted the development of endogenous timekeepers that enable an organism to reliably predict the time of day and adjust behavior and physiology accordingly. Not surprisingly, large aspects of our endocrine system are tightly connected to the circadian (from Latin *circa diem* – about a day) clock. With recent advances in molecular life sciences and medicine, we now realize that this interaction is not only unilateral but also includes endocrine feedback on circadian clock function. This review recapitulates some of the research leading to the picture we have today of the circadian clock system in mammals and provides an overview about the most prominent connection points between circadian and endocrine regulation.

The master circadian pacemaker

In the 1970s, we witnessed a significant breakthrough in the field of chronobiology – the identification of the anatomical entity underlining the mammalian circadian rhythm. It was discovered that information about the external light–dark cycle was passed via the retino-hypothalamic tract (RHT) to not only sensory input integrating centers in the thalamus, but also to the hypothalamic suprachiasmatic nucleus (SCN), hinting at the existence of a novel photic input processing hub in the brain (Sousa-Pinto & Castro-Correia 1970, Hendrickson *et al*. 1972, Moore & Lenn 1972). The SCN is a bilaterally paired structure with high cell body density located adjacent to the third ventricle and directly atop the optic chiasm. It comprises about 50 000 neurons in humans and about 20 000 neurons in rodents. A series of electrical lesion studies provided unequivocal evidence for the

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

critical role of SCN in the generation of mammalian circadian rhythms. Animals with ablated SCN become behaviorally and physiologically arrhythmic (Moore & Eichler 1972, Stephan & Zucker 1972). Critically, transplanting isolated SCN tissue into SCN-lesioned animals restores circadian rhythmicity (Ralph *et al*. 1990), and the restored behavioral rhythm of recipients is determined by the donor's intrinsic period, indicating that the SCN is indeed the master pacemaker generating circadian timing information in animals (Ralph *et al*. 1990). Brain slice explants of the SCN, but not of other tested brain areas including the cerebral cortex and arcuate nucleus, display robust circadian oscillations in firing rate *in vitro*, suggesting that the rhythmicity of the SCN is autonomous and self-sustaining (Green & Gillette 1982, Groos & Hendriks 1982, Shibata *et al*. 1982).

The molecular clockwork

The *Period* (or *Per*) gene was the first discovered clock gene (Konopka & Benzer 1971), which is conserved from fruit flies to humans. Mutations of *Per* in flies alters the circadian patterns of pupae eclosion and locomotor activity (Konopka & Benzer 1971). Since then, many more clock genes have been identified in different organisms (Zhang & Kay 2010). In the past decades, our knowledge of the molecular clockwork has been significantly expanded. The current model suggests that the central mechanism of the mammalian molecular clock is composed of a set of clock genes intertwined with a delayed interlocking transcriptional–translational feedback loop (TTL), coupled to several auxiliary mechanisms reinforcing robustness and stability (Zhang & Kay 2010). The positive limb of this TTL comprises two basic helix–loop–helix transcription factors, circadian locomotor output cycles kaput (CLOCK), and brain and muscle aryl hydrocarbon receptor nuclear translocator such as BMAL1 or ARNTL. Both form heterodimers via their PER-ARNT-SIM (PAS) domains and activate E-box-element-containing genes by recruiting transcriptional co-activators, chromatin-modifying proteins, and RNA polymerase II. In certain tissues such as the forebrain or the vasculature, CLOCK is functionally replaced by its homolog neuronal PAS domain protein 2 (NPAS2; McNamara *et al*. 2001, Reick *et al*. 2001). *Period* (*Per1–3*) and Cryptochome (*Cry1/2*) constitute the negative limb of the TTL. CLOCK–BMAL1 complexes activate the transcription of *Per* and *Cry* genes during the subjective day. PERs and CRYs translocate into the nucleus and form inhibitory complexes. With progress of the circadian cycle, PER/CRY complexes accumulate and so does their inhibitory effect on CLOCK–BMAL1 activity, shutting down *Per* and *Cry* transcription during the night (Lee *et al*. 2001). The progressive degradation of PER/CRY complexes throughout the night toward the morning releases the inhibition on CLOCK–BMAL1 transcriptional activity and thereby, completes the negative feedback loop of the circadian clock (Fig. 1).

Additional auxiliary TTLs enhance the stability of the core clock TTL and translate time-of-day information into physiological signals via transcriptional control of clock target genes (Zhang & Kay 2010). Such loops include the nuclear receptors REV–ERBα and REV–ERBβ (NR1D1 and NR1D2) and RORα (NR1F1) which regulate *Bmal1* expression via a retinoid orphan receptor responsive elements (Preitner *et al*. 2002, Ueda *et al*. 2002, Sato *et al*. 2004, Akashi & Takumi 2005, Liu *et al*. 2008), as well as the PAR basic leucine zipper proteins D-box albumin-binding protein and E4 promoter-binding protein (E4BP; NFIL3) (Cowell 2002, Ripperger & Schibler 2006) which feed-back on the expression of *Per* genes via *D-box* promoter elements (Ripperger *et al*. 2000).

Extra-SCN oscillators

The functional molecular clockwork exists not only in SCN neurons, but (almost) every single cell in the brain and periphery is capable of oscillating in a circadian manner. Molecular clock rhythms have been shown even in cultured cells, such as immortalized fibroblast cells which display robust oscillations of clock gene expression

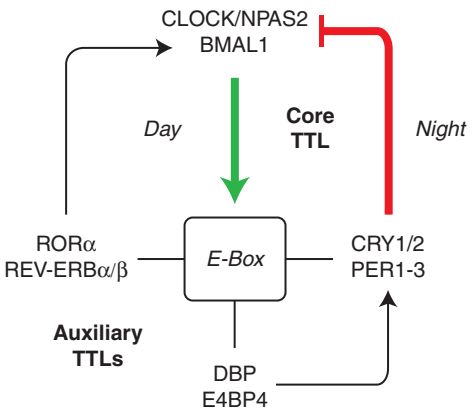

Figure 1
The molecular mammalian circadian clockwork. The transcription factors Clock/Npas2 and Bmal1 activate E-box-controlled genes including *PER1–3* and *CRY1/2* during the day. PER and CRY proteins inhibit CLOCK/BMAL1 activity during the night. Auxiliary loops stabilize this 24-h rhythm of transcriptional activation by modulating gene expression of Bmal1 and Per. For details see text.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

after a brief stimulation with high concentrations of serum (Balsalobre *et al*. 1998). Using single cell imaging techniques, Nagoshi *et al*. (2004) showed that each fibroblast cell possesses a sustained circadian clock, although at the population level the rhythm dampens quickly as a consequence of a gradual desynchronization between individual cells with different endogenous periods. Application of synchronizing agents such as serum, forskolin, glucocorticoids (GCs), or phorbol esters re-synchronizes individual cells, yielding a transiently phase-coherent population (Nagoshi *et al*. 2004). These data suggest that the cellular clocks in extra-SCN tissues are actually self-sustained and autonomous in nature, but fail to maintain coherence at the population level, in contrast to the SCN (see below). Similarly, tissue explants from a wide array of peripheral organs including heart, lung, kidney, liver, spleen, pancreas, stomach, cornea, thyroid gland, and adrenal gland show clock gene expression rhythms, but the overall rhythm dampens quickly due to the gradual loss of coherence between individual cells (Yamazaki *et al*. 2000, Yoo *et al*. 2004). Similar results have been obtained from tissue explants from various brain regions (Abe *et al*. 2002, Guilding & Piggins 2007).

SCN communication

In order to achieve a biologically relevant circadian rhythm, it is of utmost importance that individual cells of a specific tissue are synchronized to the external environment. The circadian oscillation of an SCN neuron is coupled to its neighbouring cells in an action-potential-dependent manner (Welsh *et al*. 1995). This intercellular coupling property bestows the superior robustness and resilience of the SCN circadian rhythm. For example, the SCN explant cultures exhibit robust and persistent circadian oscillations in electrophysiological activity and clock gene expression for an extended period of time, while rhythms in slices from most other brain regions and peripheral tissues dampen after a couple of days (Guilding & Piggins 2007, Guilding *et al*. 2009). SCN explant rhythms are also more resistant to clock gene mutations (Liu *et al*. 2007) and temperature fluctuations (Abraham *et al*. 2010, Buhr *et al*. 2010). One major function of the SCN is to synchronize internal biological processes to external time cues. The SCN receives photic information from both classical photoreceptors – cone and rod cells – as well as melanopsin-containing retinal ganglion cells via the RHT (Hankins *et al*. 2008). In turn, the SCN innovates other regions of the brain, in particular the hypothalamus. The paraventricular hypothalamic nucleus (PVN) is one of the major loci relaying circadian information from the SCN to the rest of the body (Saeb-Parsy *et al*. 2000). The PVN is an important integrating center for energy homeostasis, projecting parvocellular neurons to the median eminence to control the release of hormones such as adrenocorticotrophin (ACTH) and thyroid-stimulating hormone in the anterior pituitary. The PVN also innervates the sympathetic limb of the autonomous nervous system, thereby allowing the SCN to regulate the sympathetic tone of the body over the course of the day (Buijs *et al*. 2003). Further projections of the SCN to the dorsomedial hypothalamic nucleus (Luiten *et al*. 1987), the nucleus accumbens (Phillipson & Griffiths 1985) and the paraventricular thalamic nucleus (Watts & Swanson 1987, Watts *et al*. 1987) have been described. These connections enable the SCN to exert influence on a plethora of physiological processes such as the reward system, feeding-fasting cycles, cognitive function, locomotor activity, and body temperature (Dibner *et al*. 2010). In addition to direct neural connections, the SCN secretes diffusible factors, which can function as timing cues. Membrane-encapsulated foetal SCN tissue grafts, which allow only low-molecular-weight particles to diffuse, can restore the rhythmicity of locomotor activity in SCN-lesioned hamsters in the absence of axonal outgrowth (Silver *et al*. 1996). Transforming growth factor-α (Kramer *et al*. 2001, Li *et al*. 2002), prokineticin 2 (PK2; Cheng *et al*. 2002), and cardiotropin-like cytokine (Kraves & Weitz 2006) have been implicated as SCN-secreted peptides capable of regulating behavioral rhythmicity. Given the physical proximity of the SCN to the third ventricle, these diffusible factors may help propagate the time-of-day information to more remote brain regions via the cerebrospinal ventricular system.

Endocrine rhythms: clock vs behavioral regulation

It has been long been appreciated that the circulating levels of a number of hormones vary over the 24-h cycle (Andrews & Folk 1964). Such a diurnal rhythm of a hormone or metabolite can either be a manifestation of circadian clock control or a direct or indirect response to an environmental rhythm such as the light–dark cycle. Two methodologies have been developed to track down the relative contribution of the endogenous circadian clock to diurnal hormonal rhythms in humans, namely constant routine (CR) and forced desynchrony (FD) protocols. The CR protocol aims to minimize the effects of external time cues

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

and behavioral variables by equally distributing such variables across the circadian cycle. Depending on individual experimental goals, it routinely demands constant wakefulness, limited physical activity, equally distributed isocaloric snacks or constant glucose infusion and constant dim light condition (Mills *et al*. 1978). The FD protocol employs a strategy which schedules a behavioral cycle beyond the entrainable range of the circadian clock (i.e. significantly longer or shorter than 24 h) in a constant dim light environment, resulting in the free running of the endogenous circadian clock. This leads to an even distribution of certain behavioral variables in question across different phase of the circadian cycle (Kleitman 1970).

The clarification of the relative contribution of endogenous and exogenous input to the diurnal rhythm of a physiological system is of particular relevance for understanding the influence of our modern 24/7 lifestyle on the well-being of individuals. Owing to social constraints many rhythmic behaviors such as sleep/wake and food intake/fasting cycles often no longer align with their endogenous pattern controlled by the circadian clock (Scheer *et al*. 2009, Beccuti & Pannain 2011). Shift workers are an obvious example. Several epidemiological studies indicate that shift workers are predisposed for metabolic disorders and even cancer (Ohayon *et al*. 2002, Akerstedt 2003). Thus, better knowledge for the mechanistic link between circadian misalignment and hormonal deregulation may help with the development of novel medical regimes to prevent or intervene in the metabolic consequences of shift work.

GCs and melatonin represent two well-studied hormonal systems that are subject to direct and dominant regulation by the circadian clock. The circulating levels of both display robust diurnal patterns (Migeon *et al*. 1956, Ralph *et al*. 1971). Using the CR and FD experimental protocols, the secretion rhythms of cortisol (el-Hajj Fuleihan *et al*. 1997, Wehr *et al*. 2001, Aeschbach *et al*. 2003, Scheer *et al*. 2010) and melatonin (Dijk *et al*. 1999, Wehr *et al*. 2001, Cain *et al*. 2010, Gooley *et al*. 2011) have been shown to be under direct regulation by the circadian clock. Not surprisingly, both hormones also act as major hormonal output pathways that propagate the time signal from the SCN to various other tissues. In the following paragraphs, we will discuss the interaction between the central clock and these two endocrine systems.

SCN–adrenal interaction

The adrenal gland is an endocrine organ composed of two anatomically distinct structures – the cortex and medulla. The cortical part produces multiple corticosteroid hormones, while the medulla produces epinephrine and norepinephrine. The adrenal cortex is further organized into three functionally distinct subregions: the outermost zona glomerulosa producing mineralocorticoids, the middle zona fasciculata producing GCs (mainly cortisol in humans, corticosterone in rodents) and the innermost androgen-producing zona reticulata. A diurnal rhythm of the excretion of urinary ketosteroids was reported in the mid 20th century (Pincus *et al*. 1954). In the 1970s, along with the identification of the SCN as the master circadian pacemaker, the circadian secretion of corticosteroids was established as a robust hormonal output of the SCN clock (Moore & Eichler 1972, Liu *et al*. 2008). Only during the last decade, however, has the anatomical and molecular basis underlying the circadian production of corticosteroids been unveiled. Cholesterol is the precursor for the biosynthesis of steroid hormones. LDL – bound cholesterol – is imported into adrenocortical cells via LDL receptors. Cholesterol is then transported into mitochondria via steroidogenic acute regulatory protein (STAR). This import constitutes the rate-limiting step of steroidogenesis (Miller & Bose 2011). Inside the mitochondria, the side chain of cholesterol is first removed by cytochrome P450scc to become pregnenolone, which is then subjected to a series of enzyme-regulated reactions to become GC (Miller & Bose 2011). GC secretion is highly stress responsive. Together with epinephrine, GCs boost energy production and prepare the body for foraging and fight-or-flight situations. GCs exert effects on a wide array of physiological systems. In times of high energy demand, GCs help maintain blood glucose levels by promoting gluconeogenesis in liver and lipolysis in adipose tissues (Kwon & Hermayer 2013). GCs also play an important role in modulating immune (Silverman & Sternberg 2012) and cognitive functions (Sandi 2011). The majority of the effects of GCs are mediated by its ubiquitously expressed cognate nuclear receptors, glucocorticoid receptors (GRs) (Silverman & Sternberg 2012). Interestingly, despite the widespread expression pattern of GR within the brain, the SCN is devoid of GR (Okamura 2007).

The secretion of GC is the end product of hypothalamic–pituitary–adrenal (HPA) axis activation. Pituitary-released ACTH activates adrenocortical steroidogenesis through the melanocortin 2 receptor (MC2R), via a cAMP–PKA-dependent pathway which transcriptionally stimulates steroidogenic genes such as *STAR* and *CYP11A1* (Miller & Bose 2011).

Blood levels of GCs display a robust circadian rhythm, overlaid by less regular ultradian pulses with a period of

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

90–120 min. The circadian rise of GCs is phase-locked to the time of awakening, peaking at few hours before the onset of the active phase, i.e. the early morning for diurnal animals such as humans and the evening for nocturnal animals such as mice (Moore & Eichler 1972, Gomez-Abellan *et al*. 2012). This GC rise promotes arousal and boosts performance during the early active phase. Importantly, GC rhythms persist under constant environmental conditions, suggesting that they are driven by the endogenous circadian clock. Surgical ablation of the SCN completely abolishes the circadian rhythm of GC in blood, indicating that the SCN is the origin of GC rhythmicity (Moore & Eichler 1972, Stephan & Zucker 1972). HPA axis activity upstream of the adrenal is also rhythmic (Watts *et al*. 2004, Henley *et al*. 2009), which led to the hypothesis that circadian regulation of GC release may be an indirect response to SCN-induced corticotrophin-releasing hormone (CRH) expression. However, this view has been challenged by several observations. First, the timing of *CRH* expression in the hypothalamus of pro-opiomelanocortin (*POMC*; precursor peptide of ACTH) in the anterior pituitary and the plasma GC surge are not organized in the expected sequential manner (Watts *et al*. 2004, Girotti *et al*. 2009). Also, implantation of ACTH pellets can restore the rhythmicity of GC in hypophysectomized rats, while denervation of the adrenal gland abolishes the daily GC rhythm, suggesting that ACTH rhythmicity *per se* is dispensable for the blood GC rhythm (Ottenweller *et al*. 1978, Ottenweller & Meier 1982). Conversely, stimulation of adrenal sympathetic nerves results in potentiated GC responses which can be abolished by hypophysectomy (Edwards & Jones 1993), suggesting a permissive function of pituitary-derived ACTH and a more direct role of sympathetic innervation in the regulation of the circadian GC rhythm. Indeed, it has been shown in viral tracing experiments that the adrenal is connected to the SCN via the spinal cord and the PVN (Buijs *et al*. 1999). In a more recent study, it has been shown that light signals are transmitted to the adrenal cortex via the SCN, inducing an up-regulation of *PER1* expression and secretion of GC independent of ACTH (Ishida *et al*. 2005).

Well before the discovery of clock genes or peripheral clocks, it was shown that adrenal glands when isolated and cultured *in vitro* display a robust circadian rhythm of metabolism and steroid secretion (Andrews & Folk 1964). In line with this, we now know that about 5% of the whole genome – including all canonical clock genes – show rhythmic expression in the mouse adrenal gland (Oster *et al*. 2006*a*). By transplanting adrenal glands from arrhythmic *PER2/CRY1* double mutant mice to WT adrenalectomized mice, and *vice versa*, we have provided evidence that a local adrenocortical clock imposes a circadian gating mechanism altering ACTH sensitivity during the course of the day (Oster *et al*. 2006*b*). This observation was further supported in a study that used a knock down of *BMAL1* in the adrenal cortex (Son *et al*. 2008). Taken together, this illustrates that while the SCN is indispensable for the circadian rhythm of GC secretion, the adrenal clock provides an additional level of control to modulate the proficiency of GC production across the circadian cycle and further clocks along the HPA axis may be involved (Fig. 2).

SCN–pineal interaction

Unlike mice and humans, many non-mammalian vertebrates can perceive photic information by extra-retinal photoreceptors (Menaker *et al*. 1997, Foster & Soni 1998), e.g. in the pineal. The pineal gland is an ancient organ that exists in most vertebrates (Menaker *et al*. 1997). In mammals, it is buried deep beneath the skull and lies within the furrow of the two hemispheres. In consequence, its photoreceptive function is lost. However, in most cases its physiology is still strongly influenced by light. A major function of the pineal is its secretion of the hormone melatonin derived from the amino acid tryptophan (Barrett & Bolborea 2012). In mammals, melatonin exerts its effects via binding to its two widely expressed cognate receptors – MT1 and MT2. The melatonin receptors belong to the $G\alpha_i/q_i$-protein-coupled receptor superfamily (Barrett & Bolborea 2012). Owing to the widespread expression of melatonin receptors, melatonin has been reported to modulate several physiological systems such as immune function (Srinivasan *et al*. 2011), metabolism (Nduhirabandi *et al*. 2012), and higher brain functions (Srinivasan *et al*. 2012). In birds and reptiles, the pineal–melatonin system is an essential part of the circadian clockwork (Gaston & Menaker 1968, Tosini & Menaker 1998). In contrast, no overt circadian disruption is observed in pinealectomized mammals (Quay 1970, 1972), but melatonin may play an important regulatory role in distributing the time signal of the SCN (see below).

The daily pattern of melatonin secretion profile has a robust profile – being low during the day; rising and peaking during the night. In contrast to the GC rhythm which is anti-phasic in nocturnal and diurnal animals, high melatonin is always confined to the dark phase. SCN lesions abolish melatonin rhythms (Klein & Moore 1979, Reppert *et al*. 1981). The SCN connects to the

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

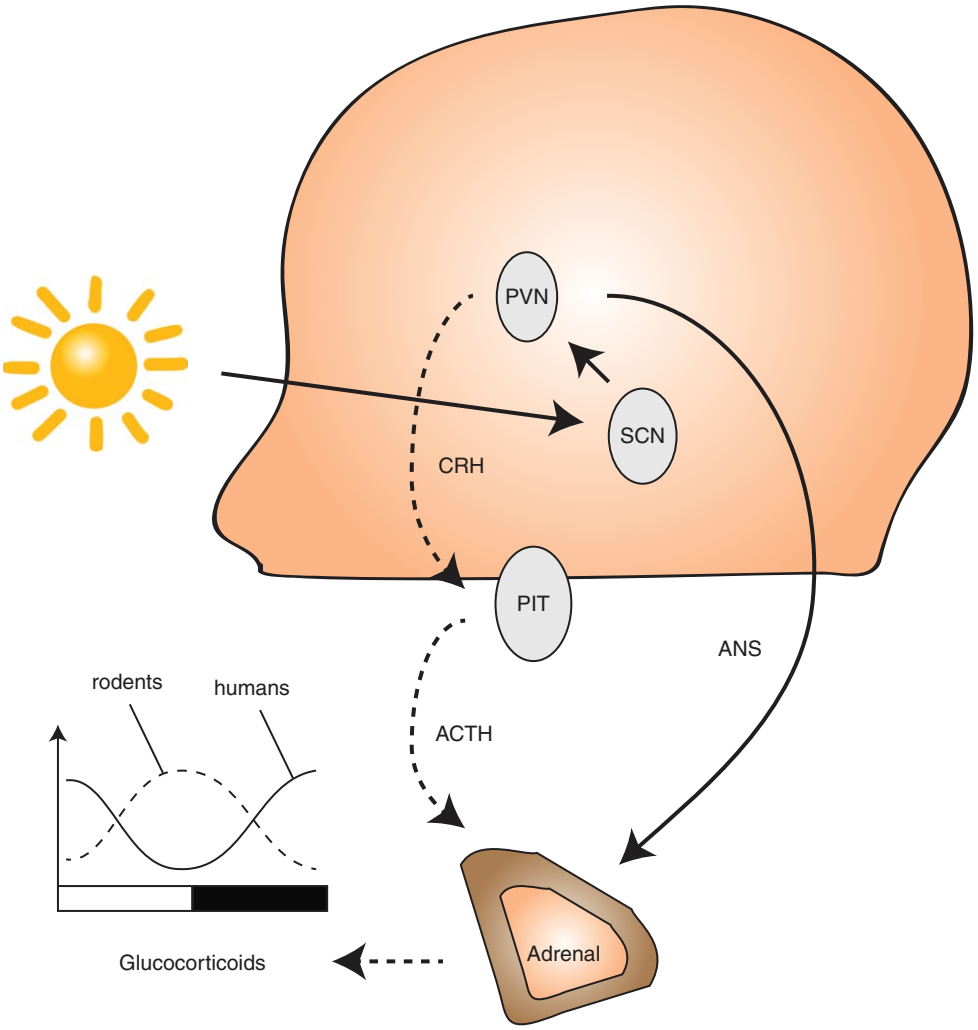

Figure 2

Interaction of central and peripheral clocks in the regulation of GC secretion. The SCN innervates the PVN from where rhythmic CRH release triggers secretion of ACTH from the pituitary (PIT). At the same time autonomic innervation (ANS) of the adrenal resets adrenocortical clocks regulating sensitivity of the steroidogenic machinery to ACTH. Synchrony between HPA axis activity and adrenal ACTH gating results in high amplitude and robust circadian GC rhythms. GC rhythms are phase-shifted between nocturnal and diurnal species indicating differential interpretation of SCN signals at downstream targets.

pineal gland via a multi-synaptic autonomic pathway which sequentially involves the PVN and then the pre-ganglionic neurons of the intermediolateral cell column of the spinal cord and finally the noradrenergic sympathetic neurons of the superior cervical ganglion (Drijfhout *et al.* 1996, Moore 1996, Larsen *et al.* 1998, Teclemariam-Mesbah *et al.* 1999; Fig. 3). The SCN releases GABA to inhibit the sympathetic input to the pineal gland during the daytime while this inhibition is released during the night (Kalsbeek *et al.* 2000). In addition, the SCN sends a constant glutamatergic stimulatory input to the pineal gland which is overwhelmed by the inhibitory mechanism during the night (Perreau-Lenz *et al.* 2004).

The role of clock genes in regulating pineal gland rhythmicity has received little attention, mainly due to the fact that many of the mouse genetic models used to study the function of the molecular clock are maintained on genetic backgrounds carrying mutations in two key enzymes of melatonin synthesis, arylalkylamine *N*-acetyltransferase (AANAT) and hydroxyindole-*O*-methyltransferase (HIOMT), resulting in melatonin deficiency (Goto *et al.* 1989, Roseboom *et al.* 1998, Vivien-Roels *et al.* 1998). *Clock*-Δ19 mutants (Vitaterna *et al.* 1994) were

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

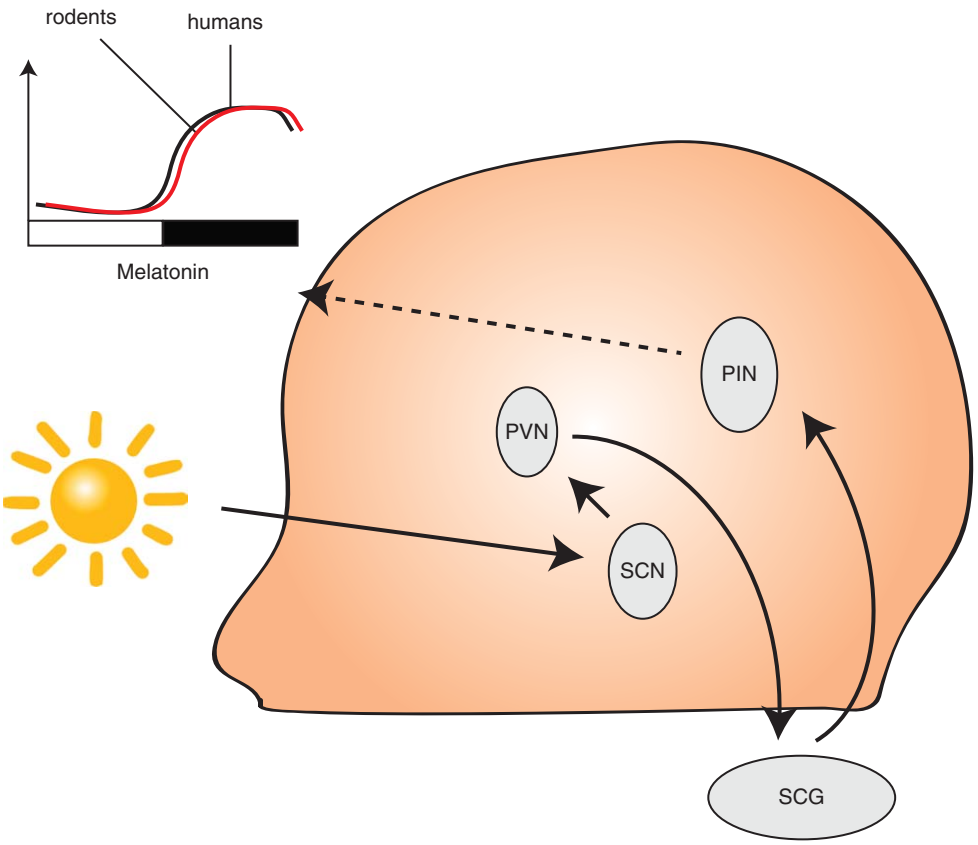

Figure 3

Melatonin release from the pineal is driven by the SCN pacemaker. The SCN innervates the PVN from where autonomous fibres descend into the spinal cord and out via the superior cervical ganglia (SCG) to reach the pineal gland (PIN). Clock genes are expressed in the pineal, but a functional contribution of a potential pineal clock to melatonin production has not been demonstrated. Unlike GCs, melatonin secretion is always confined to the dark phase, regardless of the activity profile of the animal.

back-crossed into a melatonin-proficient strain, showing that the *Clock*-Δ19 mutation leads to phase delays and dampening of the melatonin rhythm in constant darkness conditions while GC rhythms were completely abolished (Kennaway *et al*. 2003, 2006). More recently, it has been demonstrated that the melatonin biosynthesis pathway can genetically suppress the circadian perturbations of *Clock*-Δ19 mutation (Shimomura *et al*. 2010), suggesting a role of melatonin in contributing to the robustness of the SCN clock (see below). *PER1* deficiency has been shown to enhance *Aanat* transcription, enzymatic activity and hence melatonin secretion (Chen & Baler 2000, Christ *et al*. 2010). In *CRY1/2* double-deficient mice on a melatonin-proficient genetic background not only is the melatonin rhythm blunted under light–dark conditions, but also photic suppression of melatonin is abolished (Yamanaka *et al*. 2010). Together, these data suggest that clock genes impinge on pineal melatonin rhythmicity. However, owing to the lack of suitable genetic models to study the tissue-specific function of clock genes in melatonin-proficient strains, the physiological role of the molecular clock in the pineal itself remains largely unclear.

Hormonal feedback to the circadian clock

The stabilizing role of melatonin in SCN regulation mentioned above suggests that hormonal rhythms – we have discussed circadian regulation of GC and melatonin secretion – are not merely an output of the central clock. They can also feedback to the various levels of the circadian system and thereby intervene the circadian rhythm of physiology and behavior of animals (Fig. 4). In the following section, we will use these and some other hormones as examples to illustrate the crosstalk within the clock–hormones circuitry in mammals.

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

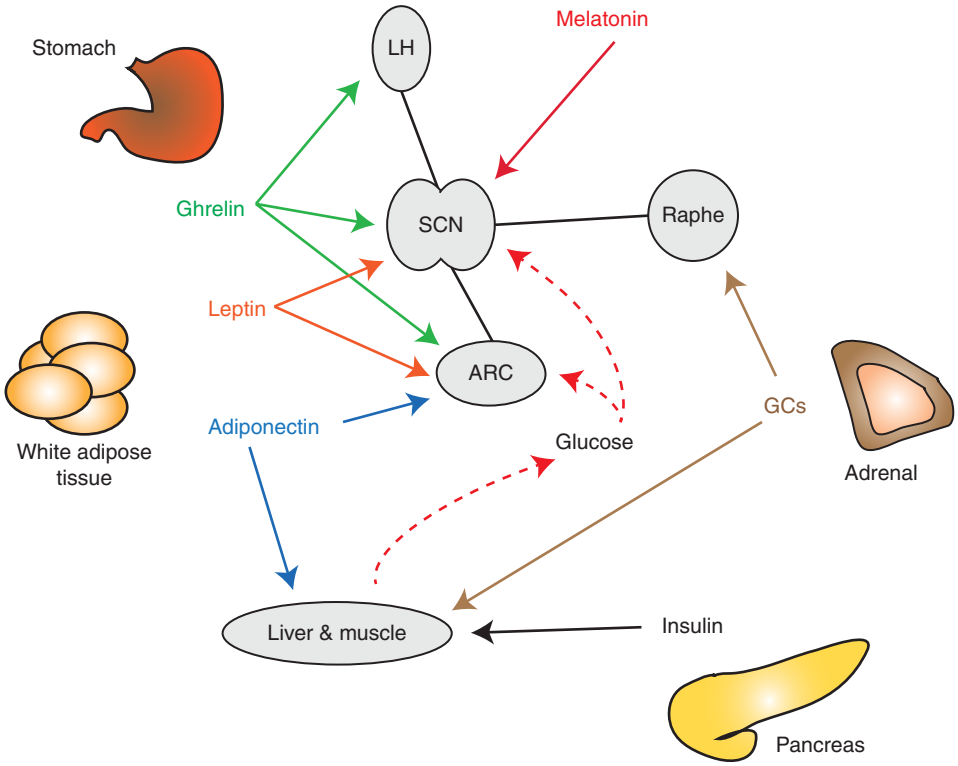

Figure 4

Endocrine feedback to the circadian clock. Various hormones can directly or indirectly feedback on central and peripheral clock function. In the brain endocrine targets with connections to the SCN include the orexinergic neurons of the lateral hypothalamus (LH), the arcuate nucleus (ARC), and the raphe nuclei of the brainstem. Other endocrine effects may be mediated via peripheral tissues and clocks such as the liver and muscle. For details see text.

Cortisol

Exposure to jetlag or sleep perturbations (such as sleep restriction or shift work) results in a transient mismatch between the internal circadian time and the external light–dark cycle. Symptoms of jetlag include decreased alertness, motor coordination and cognitive performance, sleep disturbances, gastrointestinal disruption, and loss of appetite (Waterhouse *et al.* 2005). Sleep restriction and daytime sleep – hallmarks of a night shift work schedule – are associated with increased BMI and risk of metabolic syndrome, and alterations in circulating endocrine parameters such as insulin, glucose, and GCs (Wu *et al.* 2008, Rehman *et al.* 2010, Baron *et al.* 2011). Cortisol rhythms are also affected by jet travel, even when only three or fewer time zones are crossed (Doane *et al.* 2010), as well as by relatively subtle advances in sleep timing (Dijk *et al.* 2012).

GC steroids secreted from the adrenal gland are integral regulators of energy metabolism as well as the response to immune challenge and stress. GC disruption is associated with a variety of disorders. Cushing's disease is characterized by excess cortisol, with symptoms including hypertension, hyperglycemia, sleep disorders, depression, and weight gain (Carroll & Findling 2010). Addison's disease, characterized by a lack of cortisol, is accompanied by symptoms of weight loss, elevated sensitivity to stress, hypotension, mood disorders, and hypoglycemia (Mitchell & Pearce 2012).

GCs have been shown to directly affect circadian clock gene expression in a number of tissues, such as white adipose tissue, liver, and kidney (Gomez-Abellan *et al.* 2012, Pezük *et al.* 2012). Adrenalectomy shortens re-entrainment in the SCN, lung, and kidney following phase shifts, suggesting that GCs may serve to stabilize the phase of peripheral clocks against external noise (Pezük *et al.* 2012). In the case of jetlag-induced circadian desynchrony, it was shown that manipulation of the GC rhythm could speed up or slow down activity adaptation to the new light–dark schedule, depending on the intervention time (Kiessling *et al.* 2010). This study

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

highlights the exciting therapeutic potential of GCs in the treatment of jetlag and other desynchrony disorders.

Melatonin

The best-studied physiological effect of melatonin is its modulatory function on sleep/wake cycle regulation in humans. Application of exogenous melatonin has been shown to decrease the latency to sleep, increase total sleep time, and promote sleep maintenance (Sack *et al*. 1997, Sharkey *et al*. 2001). In contrast, blocking the nocturnal release of melatonin by suppressing the sympathetic innervation to the pineal results in increased total wake time (Van Den Heuvel *et al*. 1997). Moreover, exogenous melatonin can influence sleep macro architecture (Dijk *et al*. 1995, 1997). Because of its sleep-promoting effect, melatonin treatment is frequently used to ameliorate the symptoms of jetlag or to improve sleep quality during the daytime in night-shift workers (Aeschbach *et al*. 2009).

Beyond its effect on sleep, melatonin has been shown to directly signal to the SCN. In contrast to GRs (see above), high densities of MT1 and MT2 receptors in the SCN have been demonstrated (Gillette & McArthur 1996). In rodents, timed daily administration of high concentrations of exogenous melatonin can entrain the free-running endogenous rhythm under constant darkness conditions (Armstrong *et al*. 1986, Redman & Armstrong 1988). Similarly, timed application of melatonin can entrain blind human subjects (Arendt & Broadway 1987, Sack *et al*. 2000). *In vitro*, melatonin application to cultured SCN explants affects amplitude and phase of the circadian rhythm of neuronal firing (Liu *et al*. 1997, Shimomura *et al*. 2010). The acute inhibitory effect of melatonin on neuronal activity seems to be mediated by MT1 receptor (Liu *et al*. 1997), while the phase-resetting effect relies on MT2 receptor signalling (Hunt *et al*. 2001). It is worthy of mention that melatonin is also capable of modulating the production of adrenal GCs. In humans and monkeys, acute melatonin administration suppresses the production of cortisol (Torres-Farfan *et al*. 2003, Campino *et al*. 2011). More recently, it has been demonstrated using foetal rats that timed melatonin application can entrain adrenal gland rhythms (Torres-Farfan *et al*. 2011). Thus, together melatonin and GC rhythms appear to stabilize circadian phase and precision for different physiological systems.

Ghrelin and insulin

The timing of food intake is an important entrainment signal for peripheral clocks, best characterized in, but not limited to, the liver and adipose clocks (Stephan 2002). Anticipatory behavior just before scheduled feeding (food anticipatory activity (FAA)) is seen in animals with restricted access to food. This is characterized by increased activity and changes to body temperature, GC rhythms and hepatic P450 enzymatic function (Krieger *et al*. 1977, Hirao *et al*. 2006), which function to prepare the body for the anticipated food intake. When food access is confined to the normal rest period, these processes can uncouple peripheral oscillators from the central clock that stays locked to the light regimen. Ghrelin is secreted in anticipation of feeding, regardless of the light–dark cycle, from gastric oxyntic gland cells which possess a functional clock (LeSauter *et al*. 2009). Ghrelin stimulates appetite via its actions on the hypothalamic orexigenic peptides, neuropeptide Y and orexin, and on mesolimbic reward centres (Abizaid *et al*. 2006, Toshinai *et al*. 2006). In shift workers, the post-prandial ghrelin slump is attenuated, perhaps contributing to overeating (Schiavo-Cardozo *et al*. 2012). Ghrelin administration increases FAA; however, studies on rodents lacking functional ghrelin signalling are contradictory. Mice lacking ghrelin receptors are reported to have dampened FAA (LeSauter *et al*. 2009), whilst mice lacking preproghrelin show intact FAA responses during restricted feeding (RF; Szentirmai *et al*. 2010). Ghrelin can feed back onto the circadian clock by directly affecting clock gene expression in the SCN (Yannielli *et al*. 2007). *In vivo* studies show that ghrelin treatment increases food intake, but only shifts behavioral rhythms under fasted conditions (Yannielli *et al*. 2007).

Insulin represents another potential food-inducible clock synchronizer. Insulin secretion from pancreatic beta cells is clock-gated, and disruption of the positive arm of the clock – CLOCK or BMAL1 – results in hypoinsulinemia (Marcheva *et al*. 2010, Sadacca *et al*. 2011), while disruption of the clock's negative regulators – PERs and CRYs – is associated with hyperinsulinemia (Zhao *et al*. 2012, Barclay *et al*. 2013). Insulin sensitivity is reduced in shift workers, and accompanied by increased beta cell activity, suggesting a pre-diabetic state (Esquirol *et al*. 2012). But insulin can also feed back to the clock. Tahara *et al*. (2011) used daytime RF in mice to demonstrate insulin-dependent alterations of clock gene rhythms in the liver, and a similar response was seen in primarily cultured rat hepatocytes (Yamajuku *et al*. 2012). It would be remiss to discuss the effects of insulin on the clock without discussing the effects of glucose as a direct function of insulin signalling. Glucose can directly affect circadian gene expression in fibroblasts and the SCN (Hirota *et al*. 2002, Iwanaga *et al*. 2005). In the absence of

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

insulin signalling, for example in diabetic rats, circadian clock phase is shifted in the heart, suggesting that high glucose levels can directly impinge on clock regulation (Young *et al*. 2002). Under RF conditions, sucrose (but not lipid) induces phase shifts and FAA (Stephan & Davidson 1998).

The concept of food-inducible factors acting as powerful entertainers of the clock system is ratified by a number of studies which employ RF to rescue clock gene rhythms as well as physiological rhythms under desynchronous conditions. In a rat model of night work, restricting food intake to the normal activity phase restores glucose rhythms and prevents weight gain (Salgado-Delgado *et al*. 2010). In a study on a mouse model of shift work, restoring normal food intake rhythms concurrently restores clock gene rhythmicity in the liver, as well as triglyceride, glycerol and GC rhythms, and gluconeogenesis (Barclay *et al*. 2012). While these data suggest a direct link between peripheral clock regulation and energy homeostasis, the phase relationship between clock gene expression and the transcriptional activity of metabolism-associated genes is variable, suggesting an interplay between local and systemic factors (Reznick *et al*. 2013).

Leptin and adiponectin

It is widely established that clock disruption results in metabolic perturbations, and ultimately obesity (reviewed in Froy (2010)). Conversely, high fat diet (HFD) can dampen clock gene rhythmicity in the liver and fat, and well as affecting behavioral rhythms (Kohsaka *et al*. 2007). HFD results in loss of diurnal feeding patterns in rodents, and subsequent alteration to GC, insulin, and glucose rhythms (Kohsaka *et al*. 2007). A study by Kaneko *et al*. (2009) showed altered clock gene expression the brainstem of mice fed with a HFD, as well as in genetically obese mice such as *ob/ob* (lacking the leptin gene) and KK-A(y) mice (a spontaneous diabetic mouse model). However, arguably the most dramatic effects of HFD and obesity are the effects seen on circulating adipokines such as leptin and adiponectin.

Leptin is secreted from white adipose tissue in response to glucose stimulation, and signals via appetite centres in the hypothalamus to promote satiety and prevent excess energy consumption. Circulating leptin shows a diurnal rhythm, peaking in the night in humans. In the models of obesity, leptin resistance can occur and in the absence of leptin's anorexigenic effects, this is accompanied by overeating (reviewed in Gautron & Elmquist (2011)). In humans, acute HFD feeding results in lower 24-h leptin (Havel *et al*. 1999), whereas hyperleptinemia and changes in leptin rhythmicity are observed in obese subjects in accordance with increased fat mass (Considine *et al*. 1996, Rosenbaum *et al*. 1996, van Dielen *et al*. 2002). Despite having no direct effect on locomotor activity, leptin can induce *PER* expression in the SCN of female mice and potentiate the phase-shifting effects of light in these animals (Mendoza *et al*. 2011). *Ex vivo*, leptin stimulation can reset the phase of the SCN clock (Prosser & Bergeron 2003).

Adiponectin possesses insulin-sensitizing and anti-inflammatory properties (reviewed in Harwood (2012)). Circulating adiponectin levels inversely correlate with obesity and leptin levels, and weight loss results in increased adiponectin (Hu *et al*. 1996, Yang *et al*. 2001, Matsubara *et al*. 2002). Adiponectin secretion shows both ultradian and circadian rhythms, with a nadir in the early hours of the morning in healthy adults (Gavrila *et al*. 2003, Scheer *et al*. 2010). In rodents, adiponectin peaks in the end of the light phase (inactive phase) and its rhythm is shifted under HFD (Ríos-Lugo *et al*. 2010). Bullen and colleagues showed decreased adiponectin levels relative to fat mass following HFD in rodents (Barnea *et al*. 2006, Bullen *et al*. 2007). To assess the effect of adiponectin on the circadian clock, Hashinaga and colleagues used KK-Ta mice, a polygenic model of metabolic syndrome with hypoadiponectinemia. These mice have a shorter activity period under constant conditions and dampened circadian locomotor rhythms with increased light-phase activity relative to controls. Clock gene rhythms are phase-advanced in the liver and skeletal muscle in these mice. The introduction of the human adiponectin transgene into the liver of these mice restores locomotor rhythmicity, as well as hepatic clock gene phase (Hashinaga *et al*. 2013). These studies strongly indicate that leptin, adiponectin, and maybe other adipokines may have direct effects on molecular clock function.

Summary and outlook

In summary, many components of the endocrine system show strong circadian rhythmicity in both rodents and humans. Some of these hormones, such as melatonin and cortisol, are involved in disseminating the SCN timing signal to other parts of the body. Endocrine rhythms respond to factors that compromise the clock function, such as HFD, obesity, jetlag, and sleep disruption. In turn, the endocrine system feeds back on central and peripheral clocks to adapt circadian rhythms to altered physiological state. Given the profound effects endocrine and circadian

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

systems have on general well-being and the development of various disorders, this mutual interaction might provide new targets for pharmacological interventions at the systemic level. Recent studies have shown that resetting of GC signalling can affect clock resetting during jetlag (Kiessling *et al.* 2010) and with the recent discovery of drugs directly impinging on clock function (Hirota *et al.* 2010, Solt *et al.* 2012) it may be possible to rescue endocrine regulation under desynchrony conditions such as shift work.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding

This work was supported by grants from the German Research Foundation (DFG) and the Volkswagen Foundation to H O and a Göttingen Graduate School for Neurosciences, Biophysics, and Molecular Biosciences (GGNB) fellowship from the University of Göttingen to A H T.

References

Abe M, Herzog ED, Yamazaki S, Straume M, Tei H, Sakaki Y, Menaker M & Block GD 2002 Circadian rhythms in isolated brain regions. *Journal of Neuroscience* **22** 350–356.

Abizaid A, Liu Z-W, Andrews ZB, Shanabrough M, Borok E, Elsworth JD, Roth RH, Sleeman MW, Picciotto MR, Tschöp MH *et al.* 2006 Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *Journal of Clinical Investigation* **116** 3229–3239. (doi:10.1172/JCI29867)

Abraham U, Granada AE, Westermark PO, Heine M, Kramer A & Herzel H 2010 Coupling governs entrainment range of circadian clocks. *Molecular Systems Biology* **6** 438. (doi:10.1038/msb.2010.92)

Aeschbach D, Sher L, Postolache TT, Matthews JR, Jackson MA & Wehr TA 2003 A longer biological night in long sleepers than in short sleepers. *Journal of Clinical Endocrinology and Metabolism* **88** 26–30. (doi:10.1210/jc.2002-020827)

Aeschbach D, Lockyer BJ, Dijk DJ, Lockley SW, Nuwayser ES, Nichols LD & Czeisler CA 2009 Use of transdermal melatonin delivery to improve sleep maintenance during daytime. *Clinical Pharmacology and Therapeutics* **86** 378–382. (doi:10.1038/clpt.2009.109)

Akashi M & Takumi T 2005 The orphan nuclear receptor RORα regulates circadian transcription of the mammalian core-clock Bmal1. *Nature Structural & Molecular Biology* **12** 441–448. (doi:10.1038/nsmb925)

Akerstedt T 2003 Shift work and disturbed sleep/wakefulness. *Occupational Medicine* **53** 89–94. (doi:10.1093/occmed/kqg046)

Andrews RV & Folk GE Jr 1964 Circadian metabolic patterns in cultured hamster adrenal glands. *Comparative Biochemistry and Physiology* **11** 393–409. (doi:10.1016/0010-406X(64)90006-4)

Arendt J & Broadway J 1987 Light and melatonin as zeitgebers in man. *Chronobiology International* **4** 273–282. (doi:10.3109/07420528709078534)

Armstrong SM, Cassone VM, Chesworth MJ, Redman JR & Short RV 1986 Synchronization of mammalian circadian rhythms by melatonin. *Journal of Neural Transmission. Supplementum* **21** 375–394.

Balsalobre A, Damiola F & Schibler U 1998 A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell* **93** 929–937. (doi:10.1016/S0092-8674(00)81199-X)

Barclay JL, Husse J, Bode B, Naujokat N, Meyer-Kovac J, Schmid SM, Lehnert H & Oster H 2012 Circadian desynchrony promotes metabolic disruption in a mouse model of shiftwork. *PLoS ONE* **7** e37150. (doi:10.1371/journal.pone.0037150)

Barclay JL, Shostak A, Leliavski A, Tsang AH, Johren O, Muller-Fielitz H, Landgraf D, Naujokat N, van der Horst GT & Oster H 2013 High fat diet-induced hyperinsulinemia and tissue-specific insulin resistance in Cry deficient mice. *American Journal of Physiology. Endocrinology and Metabolism* **204** E1053–E1063. (doi:10.1152/ajpendo.00512.2012)

Barnea M, Shamay A, Stark AH & Madar Z 2006 A high-fat diet has a tissue-specific effect on adiponectin and related enzyme expression. *Obesity* **14** 2145–2153. (doi:10.1038/oby.2006.251)

Baron KG, Reid KJ, Kern AS & Zee PC 2011 Role of sleep timing in caloric intake and BMI. *Obesity* **19** 1374–1381. (doi:10.1038/oby.2011.100)

Barrett P & Bolborea M 2012 Molecular pathways involved in seasonal body weight and reproductive responses governed by melatonin. *Journal of Pineal Research* **52** 376–388. (doi:10.1111/j.1600-079X.2011.00963.x)

Beccuti G & Pannain S 2011 Sleep and obesity. *Current Opinion in Clinical Nutrition and Metabolic Care* **14** 402–412. (doi:10.1097/MCO.0b013e3283479109)

Buhr ED, Yoo SH & Takahashi JS 2010 Temperature as a universal resetting cue for mammalian circadian oscillators. *Science* **330** 379–385. (doi:10.1126/science.1195262)

Buijs RM, Wortel J, Van Heerikhuize JJ, Feenstra MG, Ter Horst GJ, Romijn HJ & Kalsbeek A 1999 Anatomical and functional demonstration of a multisynaptic suprachiasmatic nucleus adrenal (cortex) pathway. *European Journal of Neuroscience* **11** 1535–1544. (doi:10.1046/j.1460-9568.1999.00575.x)

Buijs RM, van Eden CG, Goncharuk VD & Kalsbeek A 2003 The biological clock tunes the organs of the body: timing by hormones and the autonomic nervous system. *Journal of Endocrinology* **177** 17–26. (doi:10.1677/joe.0.1770017)

Bullen JW Jr, Bluher S, Kelesidis T & Mantzoros CS 2007 Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice. *American Journal of Physiology. Endocrinology and Metabolism* **292** E1079–E1086. (doi:10.1152/ajpendo.00245.2006)

Cain SW, Dennison CF, Zeitzer JM, Guzik AM, Khalsa SB, Santhi N, Schoen MW, Czeisler CA & Duffy JF 2010 Sex differences in phase angle of entrainment and melatonin amplitude in humans. *Journal of Biological Rhythms* **25** 288–296. (doi:10.1177/0748730410374943)

Campino C, Valenzuela FJ, Torres-Farfan C, Reynolds HE, Abarzua-Catalan L, Arteaga E, Trucco C, Guzman S, Valenzuela GJ & Seron-Ferre M 2011 Melatonin exerts direct inhibitory actions on ACTH responses in the human adrenal gland. *Hormone and Metabolic Research* **43** 337–342. (doi:10.1055/s-0031-1271693)

Carroll T & Findling J 2010 The diagnosis of Cushing's syndrome. *Reviews in Endocrine & Metabolic Disorders* **11** 147–153. (doi:10.1007/s11154-010-9143-3)

Chen W & Baler R 2000 The rat arylalkylamine N-acetyltransferase E-box: differential use in a master vs. a slave oscillator. *Brain Research. Molecular Brain Research* **81** 43–50. (doi:10.1016/S0169-328X(00)00160-1)

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. (doi:10.1038/417405a)

Christ E, Pfeffer M, Korf HW & von Gall C 2010 Pineal melatonin synthesis is altered in Period1 deficient mice. *Neuroscience* **171** 398–406. (doi:10.1016/j.neuroscience.2010.09.009)

Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL *et al.* 1996 Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *New England Journal of Medicine* **334** 292–295. (doi:10.1056/NEJM199602013340503)

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

Cowell IG 2002 E4BP4/NFIL3, a PAR-related bZIP factor with many roles. *BioEssays* **24** 1023–1029. (doi:10.1002/bies.10176)

Dibner C, Schibler U & Albrecht U 2010 The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annual Review of Physiology* **72** 517–549. (doi:10.1146/annurev-physiol-021909-135821)

van Dielen FM, van 't Veer C, Buurman WA & Greve JW 2002 Leptin and soluble leptin receptor levels in obese and weight-losing individuals. *Journal of Clinical Endocrinology and Metabolism* **87** 1708–1716. (doi:10.1210/jc.87.4.1708)

Dijk DJ, Roth C, Landolt HP, Werth E, Aeppli M, Achermann P & Borbely AA 1995 Melatonin effect on daytime sleep in men: suppression of EEG low frequency activity and enhancement of spindle frequency activity. *Neuroscience Letters* **201** 13–16. (doi:10.1016/0304-3940(95)12118-N)

Dijk DJ, Shanahan TL, Duffy JF, Ronda JM & Czeisler CA 1997 Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *Journal of Physiology* **505** 851–858. (doi:10.1111/j.1469-7793.1997.851ba.x)

Dijk DJ, Duffy JF, Riel E, Shanahan TL & Czeisler CA 1999 Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *Journal of Physiology* **516** 611–627. (doi:10.1111/j.1469-7793.1999.0611v.x)

Dijk DJ, Duffy JF, Silva EJ, Shanahan TL, Boivin DB & Czeisler CA 2012 Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rhythms after a gradual advance of sleep and light exposure in humans. *PLoS ONE* **7** e30037. (doi:10.1371/journal.pone.0030037)

Doane LD, Kremen WS, Eaves LJ, Eisen SA, Hauger R, Hellhammer D, Levine S, Lupien S, Lyons MJ, Mendoza S *et al.* 2010 Associations between jet lag and cortisol diurnal rhythms after domestic travel. *Health Psychology* **29** 117–123. (doi:10.1037/a0017865)

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. *Journal of Neurochemistry* **66** 748–755. (doi:10.1046/j.1471-4159.1996.66020748.x)

Edwards AV & Jones CT 1993 Autonomic control of adrenal function. *Journal of Anatomy* **183** 291–307.

Esquirol Y, Bongard V, Ferrieres J, Verdier H & Perret B 2012 Shiftwork and higher pancreatic secretion: early detection of an intermediate state of insulin resistance? *Chronobiology International* **29** 1258–1266. (doi:10.3109/07420528.2012.719959)

Foster RG & Soni BG 1998 Extraretinal photoreceptors and their regulation of temporal physiology. *Reviews of Reproduction* **3** 145–150. (doi:10.1530/ror.0.0030145)

Froy O 2010 Metabolism and circadian rhythms – implications for obesity. *Endocrine Reviews* **31** 1–24. (doi:10.1210/er.2009-0014)

Gaston S & Menaker M 1968 Pineal function: the biological clock in the sparrow? *Science* **160** 1125–1127. (doi:10.1126/science.160.3832.1125)

Gautron L & Elmquist JK 2011 Sixteen years and counting: an update on leptin in energy balance. *Journal of Clinical Investigation* **121** 2087–2093. (doi:10.1172/JCI45888)

Gavrila A, Peng C-K, 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. *Journal of Clinical Endocrinology and Metabolism* **88** 2838–2843. (doi:10.1210/jc.2002-021721)

Gillette MU & McArthur AJ 1996 Circadian actions of melatonin at the suprachiasmatic nucleus. *Behavioral Brain Research* **73** 135–139. (doi:10.1016/0166-4328(96)00085-X)

Girotti M, Weinberg MS & Spencer RL 2009 Diurnal expression of functional and clock-related genes throughout the rat HPA axis: system-wide shifts in response to a restricted feeding schedule. *American Journal of Physiology. Endocrinology and Metabolism* **296** E888–E897. (doi:10.1152/ajpendo.90946.2008)

Gomez-Abellan P, Diez-Noguera A, Madrid JA, Lujan JA, Ordovas JM & Garaulet M 2012 Glucocorticoids affect 24 h clock genes expression in human adipose tissue explant cultures. *PLoS ONE* **7** e50435. (doi:10.1371/journal.pone.0050435)

Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van Reen E, Zeitzer JM, Czeisler CA & Lockley SW 2011 Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *Journal of Clinical Endocrinology and Metabolism* **96** E463–E472. (doi:10.1210/jc.2010-2098)

Goto M, Oshima I, Tomita T & Ebihara S 1989 Melatonin content of the pineal gland in different mouse strains. *Journal of Pineal Research* **7** 195–204. (doi:10.1111/j.1600-079X.1989.tb00667.x)

Green DJ & Gillette R 1982 Circadian rhythm of firing rate recorded from single cells in the rat suprachiasmatic brain slice. *Brain Research* **245** 198–200. (doi:10.1016/0006-8993(82)90361-4)

Groos G & Hendriks J 1982 Circadian rhythms in electrical discharge of rat suprachiasmatic neurones recorded *in vitro*. *Neuroscience Letters* **34** 283–288. (doi:10.1016/0304-3940(82)90189-6)

Guilding C & Piggins HD 2007 Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? *European Journal of Neuroscience* **25** 3195–3216. (doi:10.1111/j.1460-9568.2007.05581.x)

Guilding C, Hughes AT, Brown TM, Namvar S & Piggins HD 2009 A riot of rhythms: neuronal and glial circadian oscillators in the mediobasal hypothalamus. *Molecular Brain* **2** 28. (doi:10.1186/1756-6606-2-28)

el-Hajj Fuleihan G, Klerman EB, Brown EN, Choe Y, Brown EM & Czeisler CA 1997 The parathyroid hormone circadian rhythm is truly endogenous – a general clinical research center study. *Journal of Clinical Endocrinology and Metabolism* **82** 281–286. (doi:10.1210/jc.82.1.281)

Hankins MW, Peirson SN & Foster RG 2008 Melanopsin: an exciting photopigment. *Trends in Neurosciences* **31** 27–36. (doi:10.1016/j.tins.2007.11.002)

Harwood HJ Jr 2012 The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. *Neuropharmacology* **63** 57–75. (doi:10.1016/j.neuropharm.2011.12.010)

Hashinaga T, Wada N, Otabe S, Yuan X, Kurita Y, Kakino S, Tanaka K, Sato T, Kojima M, Ohki T *et al.* 2013 Modulation by adiponectin of circadian clock rhythmicity in model mice for metabolic syndrome. *Endocrine Journal* **60** 483–492. (doi:10.1507/endocrj.EJ12-0305)

Havel PJ, Townsend R, Chaump L & Teff K 1999 High-fat meals reduce 24-h circulating leptin concentrations in women. *Diabetes* **48** 334–341. (doi:10.2337/diabetes.48.2.334)

Hendrickson AE, Wagoner N & Cowan WM 1972 An autoradiographic and electron microscopic study of retino-hypothalamic connections. *Zeitschrift für Zellforschung und Mikroskopische Anatomie* **135** 1–26. (doi:10.1007/BF00307084)

Henley DE, Leendertz JA, Russell GM, Wood SA, Taheri S, Woltersdorf WW & Lightman SL 2009 Development of an automated blood sampling system for use in humans. *Journal of Medical Engineering & Technology* **33** 199–208. (doi:10.1080/03091900802185970)

Hirao J, Arakawa S, Watanabe K, Ito K & Furukawa T 2006 Effects of restricted feeding on daily fluctuations of hepatic functions including p450 monooxygenase activities in rats. *Journal of Biological Chemistry* **281** 3165–3171. (doi:10.1074/jbc.M511194200)

Hirota T, Okano T, Kokame K, Shirotani-Ikejima H, Miyata T & Fukada Y 2002 Glucose down-regulates Per1 and Per2 mRNA levels and induces circadian gene expression in cultured Rat-1 fibroblasts. *Journal of Biological Chemistry* **277** 44244–44251. (doi:10.1074/jbc.M206233200)

Hirota T, Lee JW, Lewis WG, Zhang EE, Breton G, Liu X, Garcia M, Peters EC, Etchegaray JP, Traver D *et al.* 2010 High-throughput chemical screen identifies a novel potent modulator of cellular circadian rhythms and reveals CKIα as a Clock regulatory kinase. *PLoS Biology* **8** e1000559. (doi:10.1371/journal.pbio.1000559)

Hu E, Liang P & Spiegelman BM 1996 AdipoQ is a novel adipose-specific gene dysregulated in obesity. *Journal of Biological Chemistry* **271** 10697–10703. (doi:10.1074/jbc.271.18.10697)

Hunt AE, Al-Ghoul WM, Gillette MU & Dubocovich ML 2001 Activation of MT_2 melatonin receptors in rat suprachiasmatic nucleus phase

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

advances the circadian clock. *American Journal of Physiology. Cell Physiology* **280** C110–C118.

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

Iwanaga H, Yano M, Miki H, Okada K, Azama T, Takiguchi S, Fujiwara Y, Yasuda T, Nakayama M, Kobayashi M *et al.* 2005 Per2 gene expressions in the suprachiasmatic nucleus and liver differentially respond to nutrition factors in rats. *Journal of Parenteral and Enteral Nutrition* **29** 157–161. (doi:10.1177/0148607105029003157)

Kalsbeek A, Garidou ML, Palm IF, Van Der Vliet J, Simonneaux V, Pevet P & Buijs RM 2000 Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. *European Journal of Neuroscience* **12** 3146–3154. (doi:10.1046/j.1460-9568.2000.00202.x)

Kaneko K, Yamada T, Tsukita S, Takahashi K, Ishigaki Y, Oka Y & Katagiri H 2009 Obesity alters circadian expressions of molecular clock genes in the brainstem. *Brain Research* **1263** 58–68. (doi:10.1016/j.brainres.2008.12.071)

Kennaway DJ, Voultsios A, Varcoe TJ & Moyer RW 2003 Melatonin and activity rhythm responses to light pulses in mice with the Clock mutation. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **284** R1231–R1240. (doi:10.1152/ajpregu.00697.2002)

Kennaway DJ, Owens JA, Voultsios A & Varcoe TJ 2006 Functional central rhythmicity and light entrainment, but not liver and muscle rhythmicity, are Clock independent. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **291** R1172–R1180. (doi:10.1152/ajpregu.00223.2006)

Kiessling S, Eichele G & Oster H 2010 Adrenal glucocorticoids have a key role in circadian resynchronization in a mouse model of jet lag. *Journal of Clinical Investigation* **120** 2600–2609. (doi:10.1172/JCI41192)

Klein DC & Moore RY 1979 Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. *Brain Research* **174** 245–262. (doi:10.1016/0006-8993(79)90848-5)

Kleitman N 1970 Study wakefulness. Study the rest-activity cycle. Don't just study sleep. *International Psychiatry Clinics* **7** 381–384.

Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW & Bass J 2007 High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metabolism* **6** 414–421. (doi:10.1016/j.cmet.2007.09.006)

Konopka RJ & Benzer S 1971 Clock mutants of *Drosophila melanogaster*. *PNAS* **68** 2112–2116. (doi:10.1073/pnas.68.9.2112)

Kramer A, Yang FC, Snodgrass P, Li X, Scammell TE, Davis FC & Weitz CJ 2001 Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling. *Science* **294** 2511–2515. (doi:10.1126/science.1067716)

Kraves S & Weitz CJ 2006 A role for cardiotrophin-like cytokine in the circadian control of mammalian locomotor activity. *Nature Neuroscience* **9** 212–219. (doi:10.1038/nn1633)

Krieger DT, Hauser H & Krey LC 1977 Suprachiasmatic nuclear lesions do not abolish food-shifted circadian adrenal and temperature rhythmicity. *Science* **197** 398–399. (doi:10.1126/science.877566)

Kwon S & Hermayer KL 2013 Glucocorticoid-induced hyperglycemia. *American Journal of the Medical Sciences* **345** 274–277. (doi:10.1097/MAJ.0b013e31828a6a01)

Larsen PJ, Enquist LW & Card JP 1998 Characterization of the multisynaptic neuronal control of the rat pineal gland using viral transneuronal tracing. *European Journal of Neuroscience* **10** 128–145. (doi:10.1046/j.1460-9568.1998.00003.x)

Lee C, Etchegaray JP, Cagampang FR, Loudon AS & Reppert SM 2001 Posttranslational mechanisms regulate the mammalian circadian clock. *Cell* **107** 855–867. (doi:10.1016/S0092-8674(01)00610-9)

LeSauter J, Hoque N, Weintraub M, Pfaff DW & Silver R 2009 Stomach ghrelin-secreting cells as food-entrainable circadian clocks. *PNAS* **106** 13582–13587. (doi:10.1073/pnas.0906426106)

Li X, Sankrithi N & Davis FC 2002 Transforming growth factor-α is expressed in astrocytes of the suprachiasmatic nucleus in hamster: role of glial cells in circadian clocks. *Neuroreport* **13** 2143–2147. (doi:10.1097/00001756-200211150-00031)

Liu C, Weaver DR, Jin X, Shearman LP, Pieschl RL, Gribkoff VK & Reppert SM 1997 Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* **19** 91–102. (doi:10.1016/S0896-6273(00)80350-5)

Liu AC, Welsh DK, Ko CH, Tran HG, Zhang EE, Priest AA, Buhr ED, Singer O, Meeker K, Verma IM *et al.* 2007 Intercellular coupling confers robustness against mutations in the SCN circadian clock network. *Cell* **129** 605–616. (doi:10.1016/j.cell.2007.02.047)

Liu AC, Tran HG, Zhang EE, Priest AA, Welsh DK & Kay SA 2008 Redundant function of REV–ERBα and β and non-essential role for Bmal1 cycling in transcriptional regulation of intracellular circadian rhythms. *PLoS Genetics* **4** e1000023. (doi:10.1371/journal.pgen.1000023)

Luiten PG, ter Horst GJ & Steffens AB 1987 The hypothalamus, intrinsic connections and outflow pathways to the endocrine system in relation to the control of feeding and metabolism. *Progress in Neurobiology* **28** 1–54. (doi:10.1016/0301-0082(87)90004-9)

Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH *et al.* 2010 Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* **466** 627–631. (doi:10.1038/nature09253)

Matsubara M, Maruoka S & Katayose S 2002 Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. *European Journal of Endocrinology* **147** 173–180. (doi:10.1530/eje.0.1470173)

McNamara P, Seo SB, Rudic RD, Sehgal A, Chakravarti D & FitzGerald GA 2001 Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock. *Cell* **105** 877–889. (doi:10.1016/S0092-8674(01)00401-9)

Menaker M, Moreira LF & Tosini G 1997 Evolution of circadian organization in vertebrates. *Brazilian Journal of Medical and Biological Research* **30** 305–313. (doi:10.1590/S0100-879X1997000300003)

Mendoza J, Lopez-Lopez C, Revel FG, Jeanneau K, Delerue F, Prinssen E, Challet E, Moreau JL & Grundschober C 2011 Dimorphic effects of leptin on the circadian and hypocretinergic systems of mice. *Journal of Neuroendocrinology* **23** 28–38. (doi:10.1111/j.1365-2826.2010.02072.x)

Migeon CJ, Tyler FH, Mahoney JP, Florentin AA, Castle H, Bliss EL & Samuels LT 1956 The diurnal variation of plasma levels and urinary excretion on 17-hydroxycorticosteroids in normal subjects, night workers and blind subjects. *Journal of Clinical Endocrinology and Metabolism* **16** 622–633. (doi:10.1210/jcem-16-5-622)

Miller WL & Bose HS 2011 Early steps in steroidogenesis: intracellular cholesterol trafficking. *Journal of Lipid Research* **52** 2111–2135. (doi:10.1194/jlr.R016675)

Mills JN, Minors DS & Waterhouse JM 1978 Adaptation to abrupt time shifts of the oscillator(s) controlling human circadian rhythms. *Journal of Physiology* **285** 455–470.

Mitchell AL & Pearce SHS 2012 Autoimmune Addison disease: pathophysiology and genetic complexity. *Nature Reviews. Endocrinology* **8** 306–316. (doi:10.1038/nrendo.2011.245)

Moore RY 1996 Neural control of the pineal gland. *Behavioral Brain Research* **73** 125–130. (doi:10.1016/0166-4328(96)00083-6)

Moore RY & Eichler VB 1972 Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Research* **42** 201–206. (doi:10.1016/0006-8993(72)90054-6)

Moore RY & Lenn NJ 1972 A retinohypothalamic projection in the rat. *Journal of Comparative Neurology* **146** 1–14. (doi:10.1002/cne.901460102)

Nagoshi E, Saini C, Bauer C, Laroche T, Naef F & Schibler U 2004 Circadian gene expression in individual fibroblasts: cell-autonomous

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

and self-sustained oscillators pass time to daughter cells. *Cell* **119** 693–705. (doi:10.1016/j.cell.2004.11.015)

Nduhirabandi F, du Toit EF & Lochner A 2012 Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? *Acta Physiologica* **205** 209–223. (doi:10.1111/j.1748-1716.2012.02410.x)

Ohayon MM, Lemoine P, Arnaud-Briant V & Dreyfus M 2002 Prevalence and consequences of sleep disorders in a shift worker population. *Journal of Psychosomatic Research* **53** 577–583. (doi:10.1016/S0022-3999(02)00438-5)

Okamura H 2007 Suprachiasmatic nucleus clock time in the mammalian circadian system. *Cold Spring Harbor Symposia on Quantitative Biology* **72** 551–556. (doi:10.1101/sqb.2007.72.033)

Oster H, Damerow S, Hut RA & Eichele G 2006*a* Transcriptional profiling in the adrenal gland reveals circadian regulation of hormone biosynthesis genes and nucleosome assembly genes. *Journal of Biological Rhythms* **21** 350–361. (doi:10.1177/0748730406293053)

Oster H, Damerow S, Kiessling S, Jakubcakova V, Abraham D, Tian J, Hoffmann MW & Eichele G 2006*b* The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. *Cell Metabolism* **4** 163–173. (doi:10.1016/j.cmet.2006.07.002)

Ottenweller JE & Meier AH 1982 Adrenal innervation may be an extrapituitary mechanism able to regulate adrenocortical rhythmicity in rats. *Endocrinology* **111** 1334–1338. (doi:10.1210/endo-111-4-1334)

Ottenweller JE, Meier AH, Ferrell BR, Horseman ND & Proctor A 1978 Extrapituitary regulation of the circadian rhythm of plasma corticosteroid concentration in rats. *Endocrinology* **103** 1875–1879. (doi:10.1210/endo-103-5-1875)

Perreau-Lenz S, Kalsbeek A, Pevet P & Buijs RM 2004 Glutamatergic clock output stimulates melatonin synthesis at night. *European Journal of Neuroscience* **19** 318–324. (doi:10.1111/j.0953-816X.2003.03132.x)

Pezük P, Mohawk JA, Wang LA & Menaker M 2012 Glucocorticoids as entraining signals for peripheral circadian oscillators. *Endocrinology* **153** 4775–4783. (doi:10.1210/en.2012-1486)

Phillipson OT & Griffiths AC 1985 The topographic order of inputs to nucleus accumbens in the rat. *Neuroscience* **16** 275–296. (doi:10.1016/0306-4522(85)90002-8)

Pincus G, Romanoff LP & Carlo J 1954 The excretion of urinary steroids by men and women of various ages. *Journal of Gerontology* **9** 113–132. (doi:10.1093/geronj/9.2.113)

Preitner N, Damiola F, Lopez-Molina L, Zakany J, Duboule D, Albrecht U & Schibler U 2002 The orphan nuclear receptor REV–ERBα controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell* **110** 251–260. (doi:10.1016/S0092-8674(02)00825-5)

Prosser RA & Bergeron HE 2003 Leptin phase-advances the rat suprachiasmatic circadian clock *in vitro*. *Neuroscience Letters* **336** 139–142. (doi:10.1016/S0304-3940(02)01234-X)

Quay WB 1970 Physiological significance of the pineal during adaptation to shifts in photoperiod. *Physiology & Behavior* **5** 353–360. (doi:10.1016/0031-9384(70)90110-1)

Quay WB 1972 Pineal homeostatic regulation of shifts in the circadian activity rhythm during maturation and aging. *Transactions of the New York Academy of Sciences* **34** 239–254. (doi:10.1111/j.2164-0947.1972.tb02679.x)

Ralph CL, Mull D, Lynch HJ & Hedlund L 1971 A melatonin rhythm persists in rat pineals in darkness. *Endocrinology* **89** 1361–1366. (doi:10.1210/endo-89-6-1361)

Ralph MR, Foster RG, Davis FC & Menaker M 1990 Transplanted suprachiasmatic nucleus determines circadian period. *Science* **247** 975–978. (doi:10.1126/science.2305266)

Redman JR & Armstrong SM 1988 Reentrainment of rat circadian activity rhythms: effects of melatonin. *Journal of Pineal Research* **5** 203–215. (doi:10.1111/j.1600-079X.1988.tb00782.x)

Rehman JU, Brismar K, Holmback U, Akerstedt T & Axelsson J 2010 Sleeping during the day: effects on the 24-h patterns of IGF-binding protein 1, insulin, glucose, cortisol, and growth hormone. *European Journal of Endocrinology* **163** 383–390. (doi:10.1530/EJE-10-0297)

Reick M, Garcia JA, Dudley C & McKnight SL 2001 NPAS2: an analog of clock operative in the mammalian forebrain. *Science* **293** 506–509. (doi:10.1126/science.1060699)

Reppert SM, Perlow MJ, Ungerleider LG, Mishkin M, Tamarkin L, Orloff DG, Hoffman HJ & Klein DC 1981 Effects of damage to the suprachiasmatic area of the anterior hypothalamus on the daily melatonin and cortisol rhythms in the rhesus monkey. *Journal of Neuroscience* **1** 1414–1425.

Reznick J, Preston E, Wilks DL, Beale SM, Turner N & Cooney GJ 2013 Altered feeding differentially regulates circadian rhythms and energy metabolism in liver and muscle of rats. *Biochimica et Biophysica Acta* **1832** 228–238. (doi:10.1016/j.bbadis.2012.08.010)

Ríos-Lugo MJ, Cano P, Jiménez-Ortega V, Fernández-Mateos MP, Scacchi PA, Cardinali DP & Esquifino AI 2010 Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat–fed rats. *Journal of Pineal Research* **49** 342–348. (doi:10.1111/j.1600-079X.2010.00798.x)

Ripperger JA & Schibler U 2006 Rhythmic CLOCK–BMAL1 binding to multiple E-box motifs drives circadian Dbp transcription and chromatin transitions. *Nature Genetics* **38** 369–374. (doi:10.1038/ng1738)

Ripperger JA, Shearman LP, Reppert SM & Schibler U 2000 CLOCK, an essential pacemaker component, controls expression of the circadian transcription factor DBP. *Genes and Development* **14** 679–689. (doi:10.1101/gad.14.6.679)

Roseboom PH, Namboodiri MA, Zimonjic DB, Popescu NC, Rodriguez IR, Gastel JA & Klein DC 1998 Natural melatonin 'knockdown' in C57BL/6J mice: rare mechanism truncates serotonin N-acetyltransferase. *Brain Research. Molecular Brain Research* **63** 189–197. (doi:10.1016/S0169-328X(98)00273-3)

Rosenbaum M, Nicolson M, Hirsch J, Heymsfield SB, Gallagher D, Chu F & Leibel RL 1996 Effects of gender, body composition, and menopause on plasma concentrations of leptin. *Journal of Clinical Endocrinology and Metabolism* **81** 3424–3427. (doi:10.1210/jc.81.9.3424)

Sack RL, Hughes RJ, Edgar DM & Lewy AJ 1997 Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? *Sleep* **20** 908–915.

Sack RL, Brandes RW, Kendall AR & Lewy AJ 2000 Entrainment of free-running circadian rhythms by melatonin in blind people. *New England Journal of Medicine* **343** 1070–1077. (doi:10.1056/NEJM200010123431503)

Sadacca LA, Lamia KA, deLemos AS, Blum B & Weitz CJ 2011 An intrinsic circadian clock of the pancreas is required for normal insulin release and glucose homeostasis in mice. *Diabetologia* **54** 120–124. (doi:10.1007/s00125-010-1920-8)

Saeb-Parsy K, Lombardelli S, Khan FZ, McDowall K, Au-Yong IT & Dyball RE 2000 Neural connections of hypothalamic neuroendocrine nuclei in the rat. *Journal of Neuroendocrinology* **12** 635–648. (doi:10.1046/j.1365-2826.2000.00503.x)

Salgado-Delgado R, Angeles-Castellanos M, Saderi N, Buijs RM & Escobar C 2010 Food intake during the normal activity phase prevents obesity and circadian desynchrony in a rat model of night work. *Endocrinology* **151** 1019–1029. (doi:10.1210/en.2009-0864)

Sandi C 2011 Glucocorticoids act on glutamatergic pathways to affect memory processes. *Trends in Neurosciences* **34** 165–176. (doi:10.1016/j.tins.2011.01.006)

Sato TK, Panda S, Miraglia LJ, Reyes TM, Rudic RD, McNamara P, Naik KA, FitzGerald GA, Kay SA & Hogenesch JB 2004 A functional genomics strategy reveals Rora as a component of the mammalian circadian clock. *Neuron* **43** 527–537. (doi:10.1016/j.neuron.2004.07.018)

Scheer FA, Hilton MF, Mantzoros CS & Shea SA 2009 Adverse metabolic and cardiovascular consequences of circadian misalignment. *PNAS* **106** 4453–4458. (doi:10.1073/pnas.0808180106)

Scheer FA, Chan JL, Fargnoli J, Chamberland J, Arampatzi K, Shea SA, Blackburn GL & Mantzoros CS 2010 Day/night variations of

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

high-molecular-weight adiponectin and lipocalin-2 in healthy men studied under fed and fasted conditions. *Diabetologia* **53** 2401–2405. (doi:10.1007/s00125-010-1869-7)

Schiavo-Cardozo D, Lima MM, Pareja JC & Geloneze B 2012 Appetite-regulating hormones from the upper gut: disrupted control of xenin and ghrelin in night workers. *Clinical Endocrinology* [in press]. (doi:10.1111/cen.12114)

Sharkey KM, Fogg LF & Eastman CI 2001 Effects of melatonin administration on daytime sleep after simulated night shift work. *Journal of Sleep Research* **10** 181–192. (doi:10.1046/j.1365-2869.2001.00256.x)

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 Research* **247** 154–158. (doi:10.1016/0006-8993(82)91041-1)

Shimomura K, Lowrey PL, Vitaterna MH, Buhr ED, Kumar V, Hanna P, Omura C, Izumo M, Low SS, Barrett RK *et al.* 2010 Genetic suppression of the circadian Clock mutation by the melatonin biosynthesis pathway. *PNAS* **107** 8399–8403. (doi:10.1073/pnas.1004368107)

Silver R, LeSauter J, Tresco PA & Lehman MN 1996 A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. *Nature* **382** 810–813. (doi:10.1038/382810a0)

Silverman MN & Sternberg EM 2012 Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Annals of the New York Academy of Sciences* **1261** 55–63. (doi:10.1111/j.1749-6632.2012.06633.x)

Solt LA, Wang Y, Banerjee S, Hughes T, Kojetin DJ, Lundasen T, Shin Y, Liu J, Cameron MD, Noel R *et al.* 2012 Regulation of circadian behaviour and metabolism by synthetic REV–ERB agonists. *Nature* **485** 62–68. (doi:10.1038/nature11030)

Son GH, Chung S, Choe HK, Kim HD, Baik SM, Lee H, Lee HW, Choi S, Sun W, Kim H *et al.* 2008 Adrenal peripheral clock controls the autonomous circadian rhythm of glucocorticoid by causing rhythmic steroid production. *PNAS* **105** 20970–20975. (doi:10.1073/pnas.0806962106)

Sousa-Pinto A & Castro-Correia J 1970 Light microscopic observations on the possible retinohypothalamic projection in the rat. *Experimental Brain Research* **11** 515–527. (doi:10.1007/BF00233972)

Srinivasan V, Pandi-Perumal SR, Brzezinski A, Bhatnagar KP & Cardinali DP 2011 Melatonin, immune function and cancer. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* **5** 109–123. (doi:10.2174/187221411799015408)

Srinivasan V, De Berardis D, Shillcutt SD & Brzezinski A 2012 Role of melatonin in mood disorders and the antidepressant effects of agomelatine. *Expert Opinion on Investigational Drugs* **21** 1503–1522. (doi:10.1517/13543784.2012.711314)

Stephan FK 2002 The "other" circadian system: food as a Zeitgeber. *Journal of Biological Rhythms* **17** 284–292. (doi:10.1177/074873040201700402)

Stephan FK & Zucker I 1972 Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *PNAS* **69** 1583–1586. (doi:10.1073/pnas.69.6.1583)

Stephan FK & Davidson AJ 1998 Glucose, but not fat, phase shifts the feeding-entrained circadian clock. *Physiology & Behavior* **65** 277–288. (doi:10.1016/S0031-9384(98)00166-8)

Szentirmai E, Kapas L, Sun Y, Smith RG & Krueger JM 2010 Restricted feeding-induced sleep, activity, and body temperature changes in normal and preproghrelin-deficient mice. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **298** R467–R477. (doi:10.1152/ajpregu.00557.2009)

Tahara Y, Otsuka M, Fuse Y, Hirao A & Shibata S 2011 Refeeding after fasting elicits insulin-dependent regulation of Per2 and Rev–erbα with shifts in the liver clock. *Journal of Biological Rhythms* **26** 230–240. (doi:10.1177/0748730411405958)

Teclemariam-Mesbah R, Ter Horst GJ, Postema F, Wortel J & Buijs RM 1999 Anatomical demonstration of the suprachiasmatic nucleus–pineal pathway. *Journal of Comparative Neurology* **406** 171–182. (doi:10.1002/(SICI)1096-9861(19990405)406:2<171::AID-CNE3>3.0.CO;2-U)

Torres-Farfan C, Richter HG, Rojas-Garcia P, Vergara M, Forcelledo ML, Valladares LE, Torrealba F, Valenzuela GJ & Seron-Ferre M 2003 mt1 Melatonin receptor in the primate adrenal gland: inhibition of adrenocorticotropin-stimulated cortisol production by melatonin. *Journal of Clinical Endocrinology and Metabolism* **88** 450–458. (doi:10.1210/jc.2002-021048)

Torres-Farfan C, Mendez N, Abarzua-Catalan L, Vilches N, Valenzuela GJ & Seron-Ferre M 2011 A circadian clock entrained by melatonin is ticking in the rat fetal adrenal. *Endocrinology* **152** 1891–1900. (doi:10.1210/en.2010-1260)

Toshinai K, Yamaguchi H, Sun Y, Smith RG, Yamanaka A, Sakurai T, Date Y, Mondal MS, Shimbara T, Kawagoe T *et al.* 2006 Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. *Endocrinology* **147** 2306–2314. (doi:10.1210/en.2005-1357)

Tosini G & Menaker M 1998 Multioscillatory circadian organization in a vertebrate, *Iguana iguana*. *Journal of Neuroscience* **18** 1105–1114.

Ueda HR, Chen W, Adachi A, Wakamatsu H, Hayashi S, Takasugi T, Nagano M, Nakahama K, Suzuki Y, Sugano S *et al.* 2002 A transcription factor response element for gene expression during circadian night. *Nature* **418** 534–539. (doi:10.1038/nature00906)

Van Den Heuvel CJ, Reid KJ & Dawson D 1997 Effect of atenolol on nocturnal sleep and temperature in young men: reversal by pharmacological doses of melatonin. *Physiology & Behavior* **61** 795–802. (doi:10.1016/S0031-9384(96)00534-3)

Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, Dove WF, Pinto LH, Turek FW & Takahashi JS 1994 Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior. *Science* **264** 719–725. (doi:10.1126/science.8171325)

Vivien-Roels B, Malan A, Rettori MC, Delagrange P, Jeanniot JP & Pevet P 1998 Daily variations in pineal melatonin concentrations in inbred and outbred mice. *Journal of Biological Rhythms* **13** 403–409. (doi:10.1177/074873098129000228)

Waterhouse J, Nevill A, Finnegan J, Williams P, Edwards B, Kao SY & Reilly T 2005 Further assessments of the relationship between jet lag and some of its symptoms. *Chronobiology International* **22** 121–136. (doi:10.1081/CBI-200036909)

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. *Journal of Comparative Neurology* **258** 230–252. (doi:10.1002/cne.902580205)

Watts AG, Swanson LW & Sanchez-Watts G 1987 Efferent projections of the suprachiasmatic nucleus: I. Studies using anterograde transport of *Phaseolus vulgaris* leucoagglutinin in the rat. *Journal of Comparative Neurology* **258** 204–229. (doi:10.1002/cne.902580204)

Watts AG, Tanimura S & Sanchez-Watts G 2004 Corticotropin-releasing hormone and arginine vasopressin gene transcription in the hypothalamic paraventricular nucleus of unstressed rats: daily rhythms and their interactions with corticosterone. *Endocrinology* **145** 529–540. (doi:10.1210/en.2003-0394)

Wehr TA, Aeschbach D & Duncan WC Jr 2001 Evidence for a biological dawn and dusk in the human circadian timing system. *Journal of Physiology* **535** 937–951. (doi:10.1111/j.1469-7793.2001.t01-1-00937.x)

Welsh DK, Logothetis DE, Meister M & Reppert SM 1995 Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron* **14** 697–706. (doi:10.1016/0896-6273(95)90214-7)

Wu H, Zhao Z, Stone WS, Huang L, Zhuang J, He B, Zhang P & Li Y 2008 Effects of sleep restriction periods on serum cortisol levels in healthy men. *Brain Research Bulletin* **77** 241–245. (doi:10.1016/j.brainresbull.2008.07.013)

Yamajuku D, Inagaki T, Haruma T, Okubo S, Kataoka Y, Kobayashi S, Ikegami K, Laurent T, Kojima T, Noutomi K *et al.* 2012 Real-time monitoring in three-dimensional hepatocytes reveals that insulin acts as a synchronizer for liver clock. *Scientific Reports* **2** 439. (doi:10.1038/srep00439)

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.

Yamanaka Y, Suzuki Y, Todo T, Honma K & Honma S 2010 Loss of circadian rhythm and light-induced suppression of pineal melatonin levels in Cry1 and Cry2 double-deficient mice. *Genes to Cells* **15** 1063–1071. (doi:10.1111/j.1365-2443.2010.01443.x)

Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, Block GD, Sakaki Y, Menaker M & Tei H 2000 Resetting central and peripheral circadian oscillators in transgenic rats. *Science* **288** 682–685. (doi:10.1126/science.288.5466.682)

Yang W-S, Lee W-J, Funahashi T, Tanaka S, Matsuzawa Y, Chao C-L, Chen C-L, Tai T-Y & Chuang L-M 2001 Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *Journal of Clinical Endocrinology and Metabolism* **86** 3815–3819. (doi:10.1210/jc.86.8.3815)

Yannielli PC, Molyneux PC, Harrington ME & Golombek DA 2007 Ghrelin effects on the circadian system of mice. *Journal of Neuroscience* **27** 2890–2895. (doi:10.1523/JNEUROSCI.3913-06.2007)

Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Siepka SM, Hong HK, Oh WJ, Yoo OJ *et al.* 2004 PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *PNAS* **101** 5339–5346. (doi:10.1073/pnas.0308709101)

Young ME, Wilson CR, Razeghi P, Guthrie PH & Taegtmeyer H 2002 Alterations of the circadian clock in the heart by streptozotocin-induced diabetes. *Journal of Molecular and Cellular Cardiology* **34** 223–231. (doi:10.1006/jmcc.2001.1504)

Zhang EE & Kay SA 2010 Clocks not winding down: unravelling circadian networks. *Nature Reviews. Molecular Cell Biology* **11** 764–776. (doi:10.1038/nrm2995)

Zhao Y, Zhang Y, Zhou M, Wang S, Hua Z & Zhang J 2012 Loss of mPer2 increases plasma insulin levels by enhanced glucose-stimulated insulin secretion and impaired insulin clearance in mice. *FEBS Letters* **586** 1306–1311. (doi:10.1016/j.febslet.2012.03.034)

Received in final form 22 August 2013
Accepted 29 August 2013
Accepted Preprint published online 30 August 2013

http://jme.endocrinology-journals.org
DOI: 10.1530/JME-13-0118

Published by Bioscientifica Ltd.