Rhythms Within Rhythms: The Importance of Oscillations for Glucocorticoid Hormones

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Abstract The circadian activity of the hypothalamic-pituitary-adrenal (HPA) axis is made up from an underlying oscillatory rhythm of ACTH and glucocorticoid pulses that vary in amplitude but not frequency over the 24 h. This oscillatory activity is not the result of a hypothalamic oscillator but emerges as a natural consequence of the feedforward:feedback interaction between the pituitary corticotropes and the glucocorticoid-secreting cells of the adrenal cortex. This oscillatory activity has resulted in adaptations in the way tissues read their 'digital' ligand signal. The adrenal cortex is relatively insensitive to constant signals of ACTH but responds briskly to the equivalent amount of ACTH administered in a pulsatile manner. Similarly glucocorticoid-responsive tissues such as the brain and the liver are able to read the oscillating signals of cortisol or corticosterone secretion, with differential biochemical and functional responses to different patterns of ligand presentation. During a prolonged acute stress there is a major change in the pituitary-adrenal relationship, with a marked increase in the sensitivity of the adrenal to small changes in ACTH, so that following cardiac surgery small oscillations in ACTH result in massive swings in cortisol. This response appears to be due to a change both in the ACTH signalling pathway and in the endogenous activators and inhibitors of glucocorticoid synthesis.

Introduction

Oscillations are a basic characteristic of all matter. Atoms have their own characteristic oscillation frequencies, and the frequency of the oscillations of Cesium 133, for instance, is often chosen as the basis for atomic clocks. The kinetic theory of matter goes further to suggest that all matter is made up of particles that are constantly moving; in 1905, it was Albert Einstein who demonstrated how this

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atomic activity explained the phenomenon of Brownian movement (Einstein 1905). It is therefore of no surprise that biological systems are also invariably dynamic, with both stochastic interactions and deterministic processes across multiple time scales ensuring the maintenance of homeostatic regulation and allowing the organism to adapt to changes in both internal and external environments.

The physical world has a direct impact on the one neuroendocrine system that is critical for life: the hypothalamic-pituitary-adrenal (HPA) axis. The daily rotation of the earth on its axis provides our planet with its regular 24-h day/night cycle and this is the cue for the circadian activity of the HPA axis, which ensures energy supplies are available prior to the daily phase of activity—day in man and night in rodents—by ensuring an anticipatory increase in plasma glucocorticoid levels. These glucocorticoid hormones—cortisol in man and corticosterone in the rodent (both called CORT in this manuscript)—do not simply organise the circadian aspects of metabolic, cognitive and immunological functions, they are also vital homeostatic regulators that are extremely responsive to any threat to the organism's internal stability. In addition to their circadian variation, they need to maintain exquisite sensitivity to both perceived and genuine stressors. It is this combined function of providing a day-to-day regulatory role together with a rapid response mode that requires a system that maintains its reactivity at all times, whatever the status of its circadian activity.

How can this be achieved? The circuitry for the HPA axis is shown in Fig. 1. As has been well described by other authors in this symposium, the suprachiasmatic nucleus (SCN) of the hypothalamus provides the circadian regulation via an inhibitory input to the corticotrophin-releasing hormone (CRH)-containing neurons of the hypothalamic paraventricular nucleus (PVN) (Vrang et al. 1995; Dickmeis 2009). These neurons in turn release CRH, which travels in the hypothalamic-pituitary portal blood system to corticotroph cells in the anterior pituitary, which then release adrenocorticotropic hormone (ACTH) into the systemic circulation. Surprisingly, the output from this system is not a simple analogue release of ACTH from the pituitary gland but a complex episodic series of pulses of hormone secretion (Jasper and Engeland 1991; Windle et al. 1998). In this chapter I shall describe the mechanism underlying the genesis of this oscillating hormone system and why it is so important for the ability of glucocorticoids to perform their multiple activities in so many different systems in the body.

The Origin of HPA Pulsatility

It had always been assumed that the pulsatility of both ACTH and CORT must be due to some hypothalamic oscillator resulting in pulses of CRH, which are then transcribed into pulses of ACTH and CORT. Indeed, there is evidence for episodic release of CRH from macaque hypothalamic explants (Mershon et al. 1992) and for rapid changes in CRH in the median eminence of rats (Ixart et al. 1991) and portal blood of sheep (Caraty et al. 1988). There is, however, a mismatch between the higher frequency of CRH pulses than the ACTH/CORT pulses, and Engler

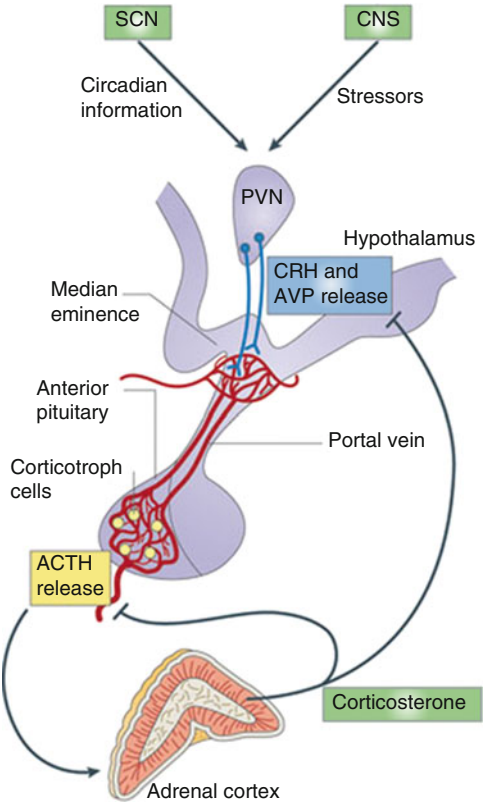

Fig. 1 The hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus receives circadian input from the suprachiasmatic nucleus (SCN) and stress-related inputs from the limbic system and brainstem. *PVN* paraventricular nucleus, *CRH* corticotrophin-releasing hormone, *AVP* arginine vasopressin. Reproduced with permission from Lightman and Conway-Campbell (2010)

et al. (1990) also demonstrated the maintenance of ACTH and cortisol pulses in the sheep even after disconnection of the pituitary from hypothalamic portal blood.

We therefore reconsidered what we knew about the interaction between pituitary corticotropes and adrenal cortical cells. Since the adrenal gland cannot store glucocorticoids—which are very lipophilic and thus cannot be stored in vesicles—every pulse of steroid released into the circulation must be newly synthesised. There must, therefore, be a delay between the signal from ACTH activation of adrenal MC2 receptors and the release of CORT. Indeed, this has been clearly demonstrated both in the rat and in man (Carnes et al. 1989; Henley et al. 2009). There is, in other words, a clear delay in the feedforward effect of ACTH on the release of CORT. What about the feedback of CORT on the pituitary corticotropes? A very rapid effect of CORT inhibiting ACTH release has been demonstrated both in the rat and in man (Jones et al. 1972; Rotsztejn et al. 1975; Hinz and Hirschelmann 2000; Russell et al. 2010). We therefore have a feedforward/feedback interaction between pituitary corticotroph-derived ACTH and adrenal cortical-derived CORT, with a built-in delay in the feedforward part of the loop. This is a system that mathematically must show endogenous oscillatory activity!

With this knowledge, we were able to collaborate with our mathematical colleagues who developed a mathematical model that predicted the ability of the pituitary adrenal system to support self-sustained ACTH and CORT oscillations at the frequency found in normal physiology, even in the face of a constant CRH drive (Walker et al. 2010). This model also predicted that these oscillations would not occur at very low CRH concentrations and would be damped at the high levels of CRH found after an acute stress, as we had found in rats following an acute stressor (Windle et al. 1998). We were then able to test this model experimentally using constant infusions of CRH into free running animals in the morning, a time when their endogenous CRH systems are suppressed by the SCN. Consistent with our mathematical model, a constant infusion of CRH produced normal ultradian oscillations of both ACTH and CORT, with the same pulse frequency as that found during normal nocturnal HPA activity (Walker et al. 2012). Furthermore, giving a constant infusion of a higher concentration of CRH resulted in a high and prolonged constant secretion of CORT, similar to that found following a severe stress.

Since circadian rhythmicity of the HPA axis is controlled by an inhibitory output from the SCN to the PVN, another prediction from our mathematical model was that interruption of this pathway would not only abolish circadian rhythmicity but would also allow unrestrained CRH secretion throughout the 24 h, resulting in ultradian secretion of ACTH and CORT throughout the 24 h and not just during times of peak activity. We tested this prediction both by lesioning of the SCN and by maintaining animals on a 24-h constant light cycle. Indeed, we found that in both cases there was a loss of circadian variability but maintenance of ultradian activity across the 24 h (Waite et al. 2012).

Implications of HPA Pulsatility

Since HPA pulsatility emerges as a natural consequence of the feedforward:feedback interaction between the pituitary and adrenal gland, it is not surprising that it has been reported to exist in all mammalian species that have been studied, including rat (Jasper and Engeland 1991; Windle et al. 1998), sheep (Fulkerson 1978), rhesus monkey (Holaday et al. 1977) and man (Weitzman et al. 1971; Henley et al. 2009). It would seem very likely, therefore, that physiological systems have adapted to read this digital ACTH and CORT signalling, and indeed this has proved to be the case.

Adrenal Adaptation to Pulsatile ACTH

Adrenal steroidogenesis is an extraordinarily dynamic process. Since steroid hormones cannot be stored for subsequent rapid release, each pulse of CORT seen in the plasma is the result of the very rapid intra-adrenal conversion of cholesterol to

CORT. Pituitary-derived ACTH binds to the melanocortin-2 receptor in adrenal fasciculata cells (Mountjoy et al. 1994), activating adenylyl cyclase and PKA-induced genomic and non-genomic steroidogenic pathways. CREB-induced transcription of the rate-limiting step of cholesterol transport into the mitochondrion (StAR) is enhanced by the binding of positive regulators (Sugawara et al. 1996; Caron et al. 1997; Song et al. 2001; Conkright et al. 2003; Takemori et al. 2007) and inhibition of the negative regulator DAX-1 (Song et al. 2004). PKA also modifies the rapid non-transcriptional modification of steroidogenic proteins, including phosphorylation of StAR itself (Arakane et al. 1997) and of hormone-sensitive lipase (HSL), which increases the intracellular levels of cholesterol itself.

So how does this complex system of different activators and inhibitors of CORT synthesis respond to different patterns of ACTH presentation? We have shown that, when endogenous ACTH is suppressed by administration of methylprednisolone, rats respond to pulsatile exogenous ACTH with a pulsatile release of CORT (Spiga et al. 2011). When the same dose of ACTH is infused at a constant rate, however, no CORT is secreted. Indeed, constant ACTH infusion actually results in a suppressed response to a subsequent stress amplitude pulse of ACTH, suggesting a dysregulation of the normal steroidogenic mechanisms (Spiga and Lightman 2014). The exact mechanism underlying this is unclear, but there is evidence that intra-adrenal GR can mediate local negative feedback on steroidogenesis via induction of DAX-1, perhaps accentuating the pulsatile characteristics of the response to a physiological pulse of ACTH while effectively inhibiting the response to a more constant exposure. Interestingly, by integrating our in vivo data with mathematical modelling of adrenal responses, we do find that rapid intra-adrenal inhibition must be an important factor in adrenal ultradian oscillations (Walker et al. 2014). This all suggests that the adrenal gland is beautifully adapted to respond to a pulsatile signal of ACTH, rather than showing a simple analogue response to different concentrations of this hormone.

During severe stress, there also seem to be special adaptations at the adrenal level. In a study of patients undergoing coronary artery bypass graft procedures (Fig. 2), we found an initial surge in both ACTH and CORT, followed by a fall in ACTH back to baseline levels but maintenance of the high levels of CORT, with continued but amplified ultradian responses of CORT to small changes in basal ACTH (Gibbison et al. 2014). The initial rise in both hormones was delayed after the actual surgery itself, suggesting it was the result of inflammatory cytokine production (from the sternotomy), which is known to go up at this time (Lahat et al. 1992; Roth-Isigkeit et al. 1999; de Mendonca-Filho et al. 2006). Therefore, in a reverse translation approach, we used a model of severe stress both with (LPS) and without (depot ACTH) associated systemic inflammation. ACTH and CORT followed each other closely in the depot ACTH-induced response, but after LPS we had the same findings as after cardiac surgery: maintenance of high CORT even after ACTH had fallen to normal levels. Furthermore, only in this group was there an increased expression of StAR and MRAP (a vital accessory for the MC2 receptor) mRNAs and StAR protein. This presumably explains the increased sensitivity to ACTH and the increased steroidogenesis at this time, which is quite

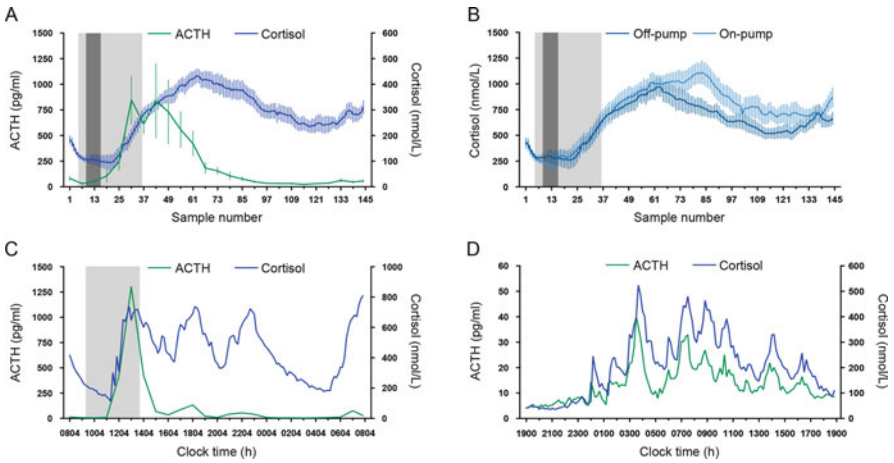

Fig. 2 Changes in cortisol and ACTH levels throughout the 24-h perioperative period of cardiac surgery. (**a**) Group mean ± SEM cortisol and ACTH. All sampling (i.e., the first sample in every case) started between 0800 and 0900 h. (**b**) Mean ± SEM 24-h cortisol profile from patients undergoing coronary artery bypass graft using the off-pump or the on-pump technique. All off-pump surgeries were performed between sample 5 and sample 35; all on-pump surgeries were performed between samples 5 and samples 36. (**a**) and (**b**), *light grey* area, period during which some patients were undergoing surgery. *Dark grey* area, period during which all patients were undergoing surgery. (**c**) Individual 24-h ACTH and cortisol profile of a patient undergoing off-pump CABG. *Light grey* area, period during which the patient was undergoing surgery (0919–1349-h). (**d**), Individual 24-h ACTH and cortisol profile of a healthy volunteer. Reproduced with permission from Gibbison et al. (2014)

different from the situation in patients who have had prolonged critical illness in whom steroidogenic genes appear to be depleted (Boonen et al. 2014).

Tissue Adaptation to Pulsatile CORT

The large oscillations of total CORT seen in blood are also reflected in similar large oscillations of the active free cortisol levels (unbound to cortisol binding globulin) in the brain and subcutaneous tissue (Droste et al. 2008; Qian et al. 2012; Bhake et al. 2013), indicating that both glucocorticoid (GR) and mineralocorticoid (MR) receptors will be exposed to oscillating levels of their ligand (Fig. 3). These receptors are latent transcription factors initially sequestered in the cytoplasm bound to chaperone molecules including HSP90 and p23. Upon binding of CORT, they undergo a conformational change dissociate from the chaperone complex and are actively transported into the nucleus where they rapidly cycle on and off glucocorticoid response elements (GREs) at the chromatin template (Fig. 4; Hager et al. 2006; Conway-Campbell et al. 2012). Each endogenous pulse of CORT results in a rapid increase in activated GR available for binding to GREs, with

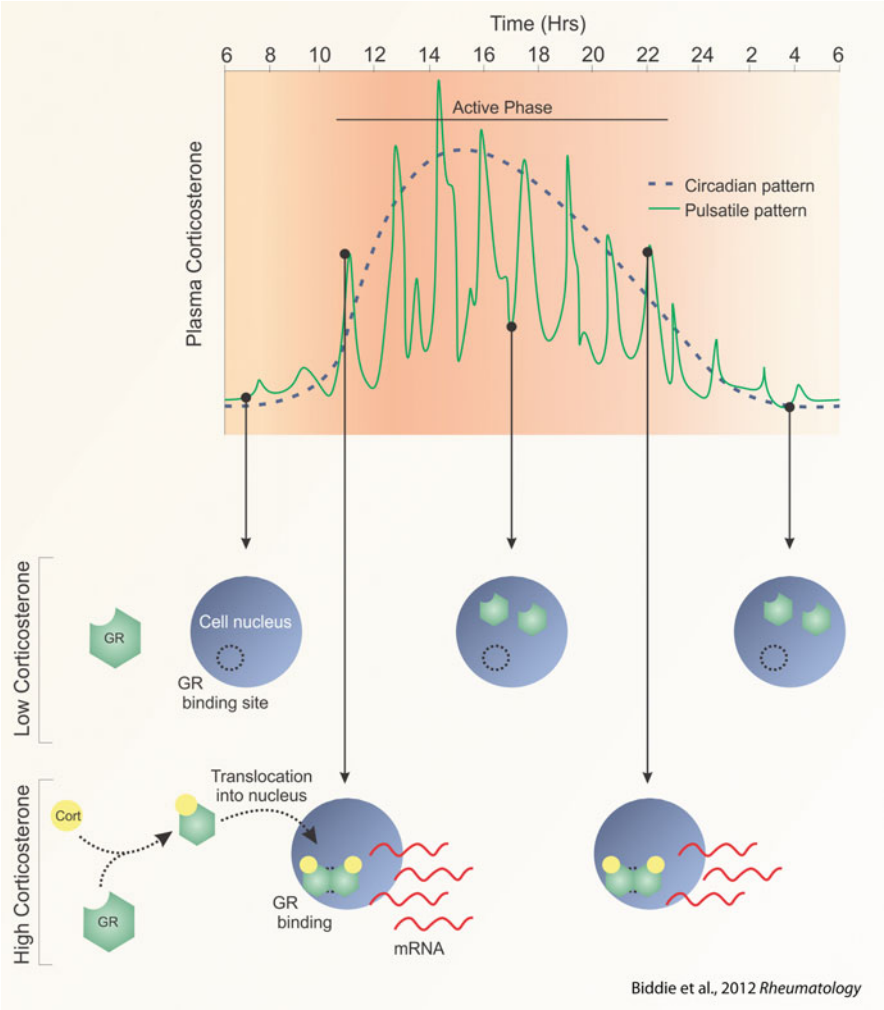

Fig. 3 Glucocorticoid pulsatility drives transient activation of GR-responsive genes. CORT levels rise in anticipation of the active phase. Hormone levels follow a circadian pattern, although the underlying pattern of hormone secretion is ultradian, where glucocorticoids are released approximately every hour. During a pulse, exposure to hormone drives GR translocation into the nucleus, where it binds to genomic elements to drive transcription. Hormone troughs result in GR dissociation from chromatin, releasing the receptor into the nucleoplasm ready to initiate transcription during further rises in hormone levels. The dynamics of the receptor and hormone secretion patterns allow rapid response to rapidly changing cellular and physiological conditions. Reproduced with permission from Biddie et al. (2011)

repeated pulses resulting in cyclical changes in GR chromatin association profiles on regulatory elements of endogenous CORT-regulated gene promoters (Fig. 4; Conway-Campbell et al. 2011). The interaction of GR with other accessory

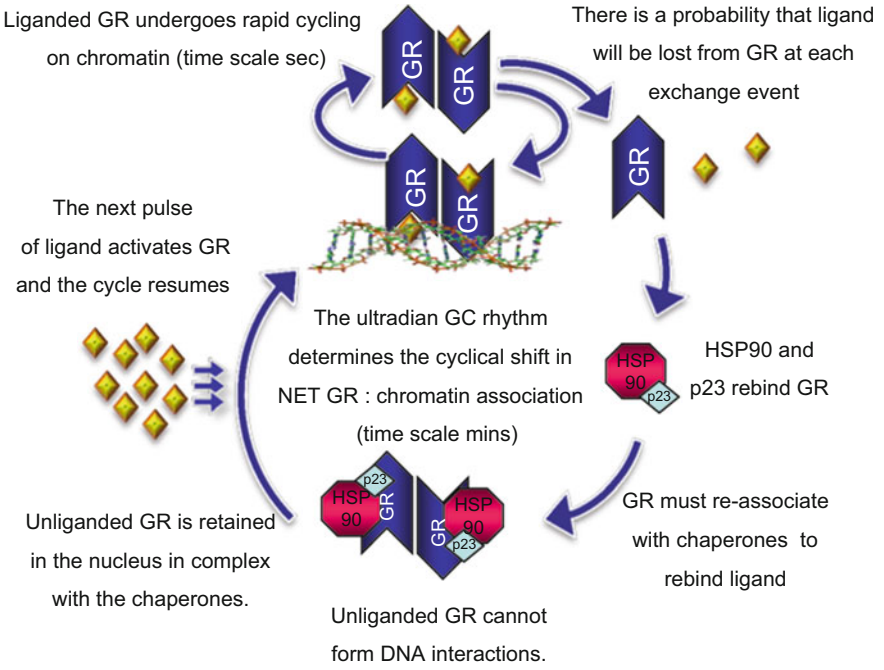

Fig. 4 GR ultradian cycling model. A schematic representation of how cyclical GR interactions with genomic response elements result in pulsatile transcriptional activity. The initial pulse of hormone causes nuclear translocation of GR, allowing GR to enter the chromatin binding cycle with rapid transient interactions with the chromatin template (stochastic action; time scale of seconds). The slower cyclical events related to the ultradian rhythm are not stochastic but are determined by pulses of ligand and the nuclear molecular chaperone cycle (time scale of minutes). Reproduced with permission from Conway-Campbell et al. (2012)

DNA-binding factors will clearly be cell and tissue specific, providing scope for differential responses to the same pattern of CORT pulses in different tissues.

There are now increasing data that ultradian pulsatility has considerable relevance for gene transcription. Ultradian oscillations of CORT induce cyclic GR-mediated pulses of gene transcription, both in vitro and in vivo, which differ from the response to equivalent constant levels of the ligand (Stavreva et al. 2009; Conway-Campbell et al. 2012; McMaster et al. 2011). Indeed, gene pulsing of the clock gene period 1 occurs in vivo in response to physiological pulses, both in the liver (Stavreva et al. 2009) and in the hippocampus (Conway-Campbell et al. 2010). In addition to these genomic effects, glucocorticoids have rapid non-genomic effects on neuronal activity in the brain (Karst et al. 2005; Evanson et al. 2010; Hill and Tasker 2012), with rapid effects on both excitatory and inhibitory inputs to the hippocampus (Karst et al. 2005), and evidence for a specific effect on the insertion of Ca^{2+}-permeable AMPA receptors into synapses (Whitehead et al. 2013). Glucocorticoid pulsatility has also been shown to have specific non-genomic effects on miniature excitatory postsynaptic current (mEPSC)

frequency in different brain areas, with differential effects being described for the amygdala and the hippocampus (Karst et al. 2010). Recently, using high-resolution imaging and electrophysiology, this group showed that, while a single pulse of CORT increases hippocampal AMPAR signalling and impairs the induction of LTP for several hours, a second pulse restores the potentiation range of the glutamate synapses (Sarabdjitsingh et al. 2014). This finding suggests that pulsatile exposure to CORT is necessary to maintain optimal glutamatergic neurotransmission.

It is also becoming clear that the pattern of glucocorticoid secretion has a considerable impact on behaviour. Adrenalectomised rats replaced with constant infusions of CORT show a blunted ACTH and behavioural response to a noise stress, whereas animals replaced with the same dose of CORT but in a physiological pulsatile pattern have normal responses (Sarabdjitsingh et al. 2010). Interestingly, these changes are associated with brain-specific differences in c-fos activation, most particularly in the amygdala, suggesting that different brain circuits respond differentially to different patterns of CORT pulsatility. This study also demonstrated a phase-dependent and region-specific response, revealing a different response during the ascending and descending phases of each CORT pulse. This finding is complementary to data from Haller et al. (2000a, b), who found that rats exposed to male intruders during a rising phase of an endogenous CORT pulse were more aggressive than rats exposed to the same stimulus on a falling phase.

The relevance of CORT pulsatility in man needs investigation. We do know that the use of non-pulsatile oral hydrocortisone replacement therapy in patients with Addisons's disease is associated with a doubling in mortality (Bergthorsdottir et al. 2006) as well as increased morbidity predominantly related to mental and physical fatigue (Løvås et al. 2002). We have now designed a technique to provide physiological CORT replacement (Russell et al. 2014) and will be using it to investigate the importance of pulsatility for optimal cognitive and metabolic function.

Conclusion

Oscillatory activity is widespread in both our physical and biological environment. At the biological level, it can occur in multiple time domains. Within the HPA there is a very rapid (seconds) interaction at the level of GR:chromatin interactions, a slower (minutes) interaction between GR and its associated chaperones, an hourly cycle that emerges as a natural consequence of subhypothalamic feedforward: feedback interactions, and a daily oscillation regulated by the SCN. The circadian variation in CORT is actually made up of changes in the amplitude of the underlying subhypothalamic ultradian rhythm. The ultradian rhythm provides digital signals for both ACTH signalling to the adrenal and CORT signalling to tissues across the whole body, including the nervous, cardiovascular, metabolic and immune systems. The body has adapted to read these signals in a tissue-specific manner, allowing one hormone to have many effects in different tissues. This

strategy of using a feedforward:feedback created digital signalling system is not unique to the HPA axis and is in fact commonly used across the endocrine system (Lightman and Terry 2014).

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