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Direct effects of the light environment on daily neuroendocrine control

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Abstract

Endocrine systems function as key mediators of adaptive responses to the external environment. As a reliable predictor of many salient variations in the external world, the light environment thus constitutes an influential source of control over neuroendocrine function. Accordingly, the vast majority of endocrine systems display 24hr variations in activity that are aligned to daily changes in external illumination. While the neural mechanisms responsible for driving these rhythms are still incompletely understood, circadian and light-dependent signals relayed via the suprachiasmatic nucleus of the hypothalamus (SCN) play a key role. Retinal projections to the SCN provide information from rods, cones and melanopsin, which, together, encode variations in the amount and spectral content of ambient light over the solar day. This sensory input, in turn, drives acute modulations in SCN cellular activity and aligns daily rhythms in the electrophysiological output of individual clock neurons. Neural outputs from the SCN can therefore convey both rapid and longer-term information about the light environment to other hypothalamic nuclei responsible for neuroendocrine control. In this review we summarises current understanding of the specific neural pathways by which the light environment influences key neuroendocrine axes, with a particular focus on the retinal and SCN-dependent circuits involved and their known sensory properties.

Introduction

As one of the key internal control mechanisms that animals use to appropriately adapt their physiology and behaviour according to the external environment, it is no surprise that the release of most, if not all, endocrine signals varies according to time of day (Czeisler and Klerman, 1999). Such observations, in large part, reflect the actions of an internal circadian timing mechanism which allows animals to proactively adjust physiology and behaviour in anticipation of the predictable changes in the outside world. In mammals, the master pacemaker for this circadian clock is the suprachiasmatic nucleus (SCN) - a hypothalamic cell group situated just above the optic chiasm. This nucleus receives input from the retina, providing information about time of day, which in turn synchronises SCN clock neurons to provide coordinated rhythmic timing signals to other key hypothalamic regions implicated in neuroendocrine and homeostatic control (Brown, 2016, Kalsbeek *et al.*, 2006).

As a result of the arrangement outlined above, changes in the light environment can result in important changes in endocrine function, both via comparatively direct circadian control of neuroendocrine systems, as well as secondary to changes in relevant behavioural cycles (e.g. rest/activity, feed/fast etc) across the 24hr day. Importantly, however, the influence of light on neuroendocrine function extends beyond the comparatively slow daily variations outlined above. Indeed, light can also much more acutely modulate the release of several hormonal signals, melatonin being the best studied example (Cajochen *et al.*, 2010). Such actions may

themselves originate with light-evoked activity in the SCN, however the existence of visual projections to other hypothalamic regions and related subcortical structures allows for various alternate possibilities.

In sum, the light environment is a major regulator of neuroendocrine function, with potentially complex underlying mechanisms that integrate circadian, visual and potentially also indirect, behaviourally mediated components (Fig. 1). In this review, we discuss current understanding of how the daily variations in the light/visual environment influence neuroendocrine function in mammals with particular reference to underlying neural mechanisms and known sensory properties of the relevant systems.

Retinal circuitry supporting effects of light on hormones

Unlike most other vertebrates, which make extensive use of extraocular photoreceptors (Peirson *et al.*, 2009), mammals rely on ocular photoreception to regulate their internal circadian clocks and coordinate daily variations in physiology and behaviour (Foster, 1998). As such, in order to understand how the visual environment impacts neuroendocrine function in mammals, it is first important to consider how light/visual signals are extracted and processed within the retina.

The retina is a highly ordered structure which performs impressive local computations to decompose the spatiotemporal distribution of incident light, detected by photoreception in the rods and cones, into a variety of distinct output 'channels'. Many of these channels are specialised to support the various facets of our visual experience of the world, such as the detection of fine-grained local variations in illumination (contrast), motion, colour etc. (Vlasits *et al.*, 2019). Importantly, however, there are also specialised retinal output pathways involved in driving subconscious (so-called non-image forming) visual responses. In particular, a key advance in our understanding of how light regulates mammalian hormonal status came with the discovery that many of the retinal output neurons innervating the SCN and other parts of hypothalamus did not require photoreception via rods or cones to be able to respond to light (Berson *et al.*, 2002). These intrinsically photosensitive ganglion cells (ipRGCs), achieve this by expressing a photopigment distinct from those in the rods and cones – melanopsin (Hattar *et al.*, 2002, Hattar *et al.*, 2003). This photopigment has slower kinetics than either rods or cones (Do *et al.*, 2009), ideally placing it to track steady changes in global light environment that occur across the day. As such, animals (including humans) that completely lack conscious vision can continue to exhibit at least some light-dependent changes in neuroendocrine function (Czeisler *et al.*, 1995, Lucas *et al.*, 1999).

While the presence of melanopsin therefore imparts a unique source of sensory control, as for the RGC classes that support more conventional aspects of vision, ipRGCs also receive synaptic inputs from other retinal cell types that convey visual signals originating with the rods and cones (Lucas *et al.*, 2014). Accordingly, in animals with an intact visual system, light dependent changes in hormone release almost certainly involve a combination of signals originating from melanopsin, rods and cones. Since each of these three photoreceptor classes has their own unique functional characteristics, determining how these various sources of visual information are integrated to define the overall sensory properties of ipRGCs and the physiological functions they control continues to be a key area of investigation.

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Of particular note, a defining feature of ipRGC visual responses is their ability to reliably track ambient light intensity over a remarkably wide range, encompassing close to the full range of light levels encountered in the natural world (Wong, 2012, Dacey *et al.*, 2005). Convergent data from rodents and primates (Dacey et al., 2005, Wong *et al.*, 2007, Weng *et al.*, 2013) suggest that this ability primarily derives from combining extrinsic rod-derived signals (which report irradiance under very low to moderate light levels) with intrinsic melanopsin dependent responses (which encode light intensity under moderate to high light intensities).

Importantly, however, in addition to the rod and melanopsin signals that appear to define their ability to encode ambient light levels, ipRGCs also receive visual information originating with cone photoreception (Dacey et al., 2005, Weng et al., 2013, Stabio *et al.*, 2018)**.** The influence of cones on the sensory properties of ipRGCs and the responses they control has proved harder to define but available evidence suggests a dual role (Brown, 2016). On one hand, the inclusion of cone signals is likely to help compensate for the very sluggish nature of melanopsin-driven photoresponses which can take several seconds to reach their maximal levels. On the other hand at least some ipRGCs (in both rodents and primates) exhibit evidence of opponent processing of signals that originate from different classes of cone photoreceptors (Dacey et al., 2005, Stabio et al., 2018). This mechanism (equivalent to that which supports our ability to discriminate blue/yellow colours) thus renders those ipRGCs capable of detecting changes in the spectral composition ('colour') of light, such as those occurring during natural twilight (Walmsley *et al.*, 2015, Spitschan *et al.*, 2017).

Collectively, the mechanisms described above (reviewed in detail previously; (Brown, 2016)) combine to allow ipRGCs to encode elements of the visual environment that are most informative regarding time of day (Fig. 2). It should be noted, however, that there is considerable heterogeneity across ipRGCs, with as many as 6 subtypes (M1-6) described in rodents (Zhao *et al.*, 2014, Quattrochi *et al.*, 2019), several of which have also been reported in primates (Hannibal *et al.*, 2017). In rodents, where ipRGC properties have been most extensively investigated, these subtypes differ in the relative contribution of melanopsin vs. rod/cone-mediated responses as well as in the presence or absence of cone-opponent responses (Zhao et al., 2014, Quattrochi et al., 2019, Stabio et al., 2018).

Further, despite a currently incomplete understanding regarding the central projection patterns of these various subtypes, there is clear evidence that the known ipRGC classes differentially innervate key visual targets in the brain (Ecker *et al.*, 2010, Hattar *et al.*, 2006, Brown *et al.*, 2010). This arrangement therefore provides a substrate by which the sensory properties of different non-image forming responses may be individually tuned based on which subtype(s) of ipRGCs (and potentially also other RGC classes) they receive input from. Of particular relevance here, retinal projections to the SCN primarily arise from the M1 subtype (Chen *et al.*, 2011), with lesser although potentially significant contributions from other RGC types (Walmsley et al., 2015, Chen et al., 2011). There are, however, also sparse ipRGC projections to other hypothalamic regions relevant for neuroendocrine control including the preoptic area, subparaventricualr zone (SPZ), and mediobasal hypothalamus (Hattar et al., 2006).

Organisation and sensory control of central clock function

As outlined above, one of the most important ways the light environment can influence neuroendocrine function is via the central circadian clock in the SCN.

In common with most cells throughout the body, SCN neurons contain a molecular clock which operates by a transcriptional-translational based feedback loop and in turn regulates the expression of a wide variety genes central to cell function (Takahashi, 2015). In the case of the SCN, these clock controlled genes include membrane ion channels, thereby generating pronounced circadian rhythms in the excitability and spontaneous electrical activity of SCN neurons (Belle and Allen, 2018). This in turn allows SCN neurons to communicate their internal representation time to other cells in the SCN and beyond.

Importantly, however, the properties of individual SCN neurons are highly heterogeneous. When cultured at low density (preventing any intercellular communication) many SCN neurons are capable of sustaining circadian rhythms in spontaneous electrical activity and gene expression but the circadian periods of those rhythms are highly variable (Welsh *et al.*, 1995, Herzog *et al.*, 2004). This period variability collapses when SCN neurons are measured in intact tissue explants, where intercellular communication allows cells to adopt a common ~24h periodicity, but is instead replaced by significant variations in phase of rhythmic activity across individual cells (Herzog et al., 2004, Brown and Piggins, 2009, Schaap *et al.*, 2003). Thus, cells with intrinsically slower clocks tend to lag behind their counterparts with naturally faster clocks in the intact network.

While the arrangement described above allows SCN neurons to generate coherent circadian timing signals, to be of use, such signals need to be appropriately aligned to the external environment. Thus, retinal input to the SCN is critical for adjusting the molecular clockwork across the SCN to precisely match the periodicity of the cycle in environmental illumination and ensuring the electrical output of the SCN neuronal ensemble is appropriately timed (Meijer and Schwartz, 2003). Of note, regardless of what temporal niche an animal occupies (nocturnal, diurnal, crepuscular), this daily peak in SCN population output appears to be timed to occur during the middle part of the light period (Schwartz *et al.*, 1983, Challet, 2007).

As discussed above for their intrinsic circadian properties, however, the influence of retinal input on SCN neurons is also heterogenous. Firstly, not all SCN neurons receive retinal input (Morin and Allen, 2006, Lokshin *et al.*, 2015). Indeed, while there seems to be considerable inter-species diversity in the precise arrangements of retinal projections, a general feature of SCN organisation seems to be the presence of a 'core' region with dense retinal input and a 'shell' region with more sparse retinal input. Secondly, among those cells presumed to receive direct retinal inputs (as evidence by rapid and acute light-evoked changes in neural activity) the influence of visual signals can differ significantly, as described below.

Acute light-dependent changes in SCN neuron activity have been described in many species (Meijer *et al.*, 1986, Meijer *et al.*, 1989, Groos and Mason, 1980, Mure *et al.*, 2007) but have only been evaluated in detail in mice and rats. As expected based on the dominant contribution of a particular class of ipRGCs (M1) to rodent SCN retinal input (Hattar et al., 2006), the majority of visually response SCN cells exhibit evidence of strong, melanopsin-dependent, sustained changes in firing with increasing light intensity (Brown *et al.*, 2011, Walmsley et al., 2015). Under appropriate conditions, clear evidence of both rod and cone driven increases in SCN neuronal activity have also been reported, although the nature of

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cones inputs varies substantially across visually responsive SCN neurons (Aggelopoulos and Meissl, 2000, Walmsley et al., 2015, Dobb *et al.*, 2017)**.** Indeed, at least in the mouse, there appears to be distinct subsets of neurons that process inputs from different classes of cone photoreceptor in an additive (achromatic) or opponent (chromatic) manner (Walmsley et al., 2015). The latter class is further subdivided into colour responsive cells that are excited by either short ('blue') or long ('yellow') wavelength light.

In sum then, SCN neurons vary both in their intrinsic circadian timekeeping properties and in their acute responses to environmental signals. In addition, while SCN neurons are GABAergic in nature, they are also neurochemically diverse, with subsets of cells expressing a wide variety of peptide co-transmitters such as arginine vasopressin (AVP), vasoactive intestinal polypeptide (VIP) and gastrin releasing peptide (GRP) (Evans, 2016). As a result of this very rich functional and neurochemical heterogeneity (Fig. 3), there is still considerable uncertainty regarding how SCN network function is organised and used to control downstream physiological systems.

In the case of overall control of SCN timing relative to the light environment (i.e. circadian photoentrainment), behavioural studies provide clear evidence for integration of the two salient environmental signals; information about brightness derived from rods and/or melanopsin and information about colour derived from cones (reviewed in (Brown, 2016)). At the cellular/network level, however, it is still unclear how the various neuroanatomically and functionally defined subsets of SCN neurons map onto one another. Nonetheless, one intriguing suggestion which has recently received clear experimental support (e.g. (Gizowski *et al.*, 2016)), is that specific subsets of SCN neurons are specialised to control distinct physiological responses (Kalsbeek et al., 2006).

The diverse nature of circadian/light-dependent signals present in the SCN potentially allows, therefore, for quite divergent impacts of the light environment on different downstream physiological systems. Importantly, in the context of this review, SCN neurons project to a variety of downstream targets that are either directly involved in the control of neuroendocrine function or well placed to indirectly influence this. Such targets include the paraventricular nuclei of the hypothalamus (PVN), dorsomedial nuclei of the hypothalamus (DMH), medial pre-optic area (MPOA), SPZ and organum vasculosum terminalis (Morin, 2013, Kalsbeek and Buijs, 2002). Beyond the hypothalamus, projections are also sent to thalamic regions implicated in relevant aspects of behavioural state control such as the paraventricular thalamus (PVT), lateral habenula and bed nucleus of the stria terminalis.

Of note here, direct SCN efferents to the hypothalamus appear to be central to the circadian control of neuroendocrine rhythms. Hence, while robust behavioural rhythms can be restored to SCN lesioned animals by transplantation of foetal SCN grafts, this manipulation does not restore neuroendocrine rhythmicity (Meyer-Bernstein *et al.*, 1999, Lehman *et al.*, 1987). Indeed, as dicussed in detail below, direct SCN projections target many of the key neurosecretory hypothalamic cell groups including corticotrophin releasing hormone (CRH), thyrotrophin releasing hormone (TRH), gonadotrophin releasing hormone (GnRH) and dopaminergic neurons (Kalsbeek et al., 2006). Further, SCN projections to pre-autonomic neurons in the PVN that are relevant for additional roles in the regulation of neuroendocrine function have been identified (Ueyama *et al.*, 1999, Buijs *et al.*, 1999, Kalsbeek *et al.*, 2000a, Larsen *et al.*, 1998).

As alluded to above, the specific properties of SCN neurons projecting to the targets outlined above remain largely unknown. For the remainder of this review, then, we highlight current understanding of how circadian/visual signals (originating in the SCN or elsewhere) influence daily patterns of neuroendocrine secretion, with a focus on those systems where there is the most currently available information.

Daily control of pineal melatonin synthesis.

Without doubt, the best studied aspect of how the light environment influences neuroendocrine function relates to the pineal hormone melatonin.

The synthesis and release of melatonin from the pineal gland is strongly rhythmic under constant (low light) conditions and is profoundly inhibited by light (Cajochen et al., 2010). As a result of this arrangement, circulating melatonin levels (which are high during the night in both nocturnal and diurnal mammals) provide information about day-length. This makes melatonin both an important systemic source of daily timing information and a key signal for the photoperiodic control of physiology in many animals (Wood and Loudon, 2018, Dardente *et al.*, 2019). Since photoperiodic mechanisms have been discussed extensively previously, we do not tackle these in detail here. Instead we focus on the organisation and sensory properties of the neural pathways regulating pineal melatonin synthesis/release.

The major anatomical pathways for the circadian/diurnal control of pineal melatonin have been known for many years, with initial investigations establishing that this required the SCN and involved sympathetic input from the superior cervical ganglion and the pineal (Klein *et al.*, 1971, Moore and Klein, 1974). Subsequent studies using transneuronal tracers further delineated this pathway, showing that the connections from the SCN pass via pre-autonomic neurons in the PVN, to preganglionic neurons in the spinal cord, and the noradrenergic neurons in the superior cervical ganglion (Kalsbeek et al., 2006, Larsen et al., 1998, Teclemariam-Mesbah *et al.*, 1999).

Ablation or inactivation of neurons at any stage of the pathway described above will impact melatonin synthesis and rhythmicity (Perreau-Lenz *et al.*, 2003, Perreau-Lenz *et al.*, 2004). Of note, however, manipulations performed at the level of the PVN or superior cervical ganglion lead to constitutively low levels of melatonin while removal of SCN input leads to constitutively high levels. This pattern is therefore suggests a model whereby clock and/or light driven increases in SCN neuronal activity inhibits pre-autonomic PVN neurons involved in regulating melatonin synthesis. Consistent with this view, infusion of a GABA receptor antagonist into the PVN and surrounding areas causes an increase of daytime melatonin concentrations and blocks light-induced nocturnal suppressions (Kalsbeek *et al.*, 2000b, Kalsbeek *et al.*, 1999).

While the neural circuits responsible for the daily control of pineal melatonin release are thus well established (Fig. 4), attaining a detailed understanding of the sensory signals that regulate this has proved more challenging. This, in part, likely reflects the challenges associated with obtaining detailed measures of the sensory control of melatonin synthesis in rodents. Nonetheless, by the late 1990's, convergent evidence from humans and mice revealed that light-dependent melatonin suppression persisted in the absence of functional rod/cone photoreception suggesting the involvement of a novel photopigment (Freedman *et al.*, 1999,

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Czeisler et al., 1995). While we now know this is due to the central role of ipRGCs/melanopsin in conveying light information to the SCN (Guler *et al.*, 2008) there has remained some uncertainty regarding the sensory influences on melatonin synthesis. In particular, the majority of available data across rodent and primate models indicates melanopsin has a peak spectral sensitivity in the region of 480nm (Lucas *et al.*, 2001, Berson et al., 2002, Dacey et al., 2005, Bailes and Lucas, 2013). By contrast, two independent initial reports suggested that the peak spectral sensitivity for melatonin suppression in humans was substantially different from this value (Brainard *et al.*, 2001, Thapan *et al.*, 2001).

More recent studies (including re-evaluation of some of the earlier data) do place the spectral sensitivity of melatonin suppression firmly in the vicinity of 480, confirming a dominant role for melanopsin (Najjar *et al.*, 2014, Prayag *et al.*, 2019). Nonethelss, it should also be noted that, while melanopsin photoreception alone seems to well-predict the effects of long duration light exposures on melatonin, there is also clear evidence for the involvement of cone photoreception. Indeed, evaluation of the spectral sensitivity of initial light-evoked changes in circulating melatonin suggests a much more dominant role for cones (Gooley *et al.*, 2010). Some previous studies have also suggested the possibility of colour–opponent regulation of melatonin release in humans (Figueiro *et al.*, 2008, Figueiro *et al.*, 2004), although there is conflicting data in this regard (Revell and Skene, 2007, Papamichael *et al.*, 2012). Full confirmation on this point therefore requires additional studies employing chromatic stimuli appropriately controlled for their impact on melanopsin.

One final point to note here is that, despite the central role for the SCN in the control of melatonin synthesis, the sensory mechanism by which light influences this neuroendocrine signal do not exactly recapitulate those of the circadian entrainment mechanism. This includes clear differences in the relative sensitivity to short vs. long wavelength light (Gooley et al., 2010) as well as differences in the response to continuous vs. intermittent light steps (Rahman *et al.*, 2018). For example, the latter study reveals that, whereas a series of six 15min bright light pulses spread over 6.5h suppresses melatonin much less than 6.5h of continuous illumination, the two stimuli appear to evoke very similar effects on the circadian phase. Such discrepancies likely reflect processing that occurs within the SCN network downstream of the acute light-dependent changes in activity that are used to acutely regulate melatonin synthesis.

Daily control of the hypothalamic-pituitary-adrenal axis

Unlike melatonin, which is strongly tied to the night time in all mammals, activity of the hypothalamic-pituitary-adrenal (HPA) axis is closely aligned to the animals' behavioural patterns to provide maximal glucocorticoid release just prior to the onset of activity (Kalsbeek *et al.*, 2012). As a result, the (comparatively less well understood) mechanisms by which circadian and light-dependent signals influence HPA activity likely differ somewhat between nocturnal and diurnal mammals.

The HPA axis itself consists of neurons in the medial PVN, which release CRH. These target corticotrophs in the anterior pituitary gland, which in turn release adrenocorticotrophic releasing hormone (ACTH) into the blood stream where it acts on the adrenals to drive

glucocorticoid secretion. The circulating cortisol/corticosterone (CORT) then feeds back to downregulate HPA activity (Gjerstad *et al.*, 2018). Collectively, HPA axis activity then produces a pulsatile (ultradian) pattern of CORT secretion whose amplitude is strongly modulated by circadian signals from the SCN (Moore and Eichler, 1972, Waite *et al.*, 2012). There are now a number of identified and potentially convergent mechanisms by which the output from the SCN clock may achieve this regulation (Fig. 5).

Based on a series of microdialysis studies in rats, Kalsbeek, Buijs and colleagues suggest a central role for AVP cells of the SCN in driving daily rhythms in HPA axis activity (Kalsbeek et al., 2012). By their model, AVP release from the SCN during the early to mid-day activates GABAergic neurons in the DMH and/or SPZ, which in turn inhibit CRH neurons in the PVN, to keep circulating CORT levels low. Consistent with this view, infusion of a V_1 receptor antagonist into the DMH substantially enhances HPA axis activity during early-mid portions of the day, while infusion of AVP supresses the evening rise in CORT (Kalsbeek *et al.*, 1996a, Kalsbeek *et al.*, 1996b). Nonetheless, the continued presence of rhythms in HPA axis activity while AVP signalling to the DMH is blocked also suggest the presence of additional factors regulating daily glucorticoid rhythmicity. The existence of direct SCN projections to CRH neurons provides one such route by which this may be achieved (Vrang *et al.*, 1995). In addition, however, neuroanatomical tracing studies reveal the presence of SCN neurons that are multisynaptically connected to the adrenal via pre-autonomic PVN neurons (Buijs et al., 1999, Ueyama et al., 1999). Via this pathway, the SCN might also regulate CORT secretion by adjusting adrenal sensitivity to circulating ACTH (Kaneko *et al.*, 1980, Kaneko *et al.*, 1981, Jasper and Engeland, 1994).

Interestingly, by contrast to the pronounced inhibitory effect of SCN output on HPA activity described above, several studies indicate that light exposure enhances levels of circulating CORT in rodents (Ishida *et al.*, 2005, Rahman *et al.*, 2008, Loh *et al.*, 2008, Kiessling *et al.*, 2014). This effect is not associated with detectable changes in plasma ACTH, but is accompanied by increases in adrenal sympathetic nerve activity and a significant induction of gene expression across the adrenals (Ishida et al., 2005, Kiessling et al., 2014). Since this effect of light is abolished by SCN lesion (Ishida et al., 2005), it is assumed to involve SCN-dependent stimulation of the autonomic nervous system, via a pathway similar to that described above. VIP expressing cells of the SCN have been suggested as a potential mediator of this effect since mice lacking VIP display greatly attenuated light-driven increases in circulating CORT (Loh et al., 2008). It should be noted, however, that the loss of VIP induces a pronounced global disruption to SCN function (Colwell *et al.*, 2003, Aton *et al.*, 2005, Maywood *et al.*, 2006, Brown *et al.*, 2007), leaving a specific role for VIP cells in such an effect uncertain.

In summary, there appears then to be at least two different routes by which SCN activity can influence circulating CORT levels in rodents. A circadian control which impinges on CRH neurons to drive rhythms in ACTH secretion (Kalsbeek et al., 1996b, Loh et al., 2008) and a light dependent process which involves activation of sympathetic input to the adrenals (Ishida et al., 2005). Although the sensory properties of this latter pathway have not yet been investigated in detail, it appears to require relatively high light levels to produce noticeable impacts (Kiessling et al., 2014), in stark contrast to the much higher sensitivity of circadian photoentrainment responses (Lall *et al.*, 2010). Given the relatively high light levels required

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and the requirement for an intact SCN, it seems likely that melanopsin signals relayed by ipRGC projections to the SCN (or nearby regions) play a major role in the effects of light on CORT. Consistent with this possibility, white light sources lacking significant energy in portions of the spectrum where melanopsin is most sensitive (460-480nm) are remarkably less effective at stimulating CORT secretion in rats (Rahman et al., 2008). This latter study does not provide conclusive evidence for the role of melanopsin, however, since other photoreceptors in the rat (rods and medium-wavelength sensitive cones) also show high sensitivity in this portion of the visible spectrum.

By comparison to the rodent data outlined above, there is considerably less mechanistic understanding of circadian and diurnal sources of control over HPA axis activity in diurnal animals. Hence, while the timing of SCN clock output and its response to light is similar between nocturnal and diurnal mammals, rhythms in circulating CORT are phase inverted (Perlow *et al.*, 1981, Schwartz et al., 1983, Challet, 2007). In general, such differences are considered to reflect an inversion of the impact of SCN derived signals on downstream brain regions (Sato and Kawamura, 1984, Brown and Piggins, 2007). However, as far as we are aware, there have not yet been any direct investigations of how SCN output influences HPA axis activity in fully diurnal animals.

In general accord with the idea that SCN outputs should have opposite effects on HPA axis activity in diurnal vs. nocturnal animals, studies in a crepuscular/diurnal rodent (*Arvicanthis ansorgei*) do provide convincing evidence for a reversal in the role of endogenous AVP signalling (Kalsbeek *et al.*, 2008). Hence, this latter work reveals that endogenous AVP signalling in the PVN/DMH region is required for morning and evening surges in circulating CORT in *Arvicanthis*, by contrast to the suppressive daytime effects seen in rats (Kalsbeek et al., 1996b). Whether this apparent stimulatory action reflects a crepuscular pattern of AVP release from the *Arvicanthis* SCN itself remains unclear, however. Similarly, there is no concrete information regarding differences in the underlying neural circuitry that could produce the inversion of AVP effects relative to those seen in rats. The assumption is that AVP output from the SCN targets excitatory rather than inhibitory DMH interneurons in *Arvicanthis* (Kalsbeek et al., 2008), although a more direct stimulation of CRH cells in the PVN in this species seems a plausible alternative mechanism.

In either case, given the apparent reversal in the impact of SCN-derived circadian signals on HPA axis activity in nocturnal and diurnal animals, one might expect a similar reversal in the acute response of this system to light. In fact, current literature is rather equivocal on this point. While there have certainly been some studies demonstrating light induced reductions in CORT levels in humans (Kostoglou-Athanassiou *et al.*, 1998, Jung *et al.*, 2010) there have also been many showing light-induced increases (Scheer and Buijs, 1999, Leproult *et al.*, 2001, Figueiro and Rea, 2010, Gabel *et al.*, 2013, Petrowski *et al.*, 2019). The origin of these discrepancies remains unclear. Nonetheless, it is noteworthy that light-stimulated changes in CORT in nocturnal rodents seem to involve a different pathway that that underlying circadian changes. In this regard, it is possible that, while mechanisms of circadian control diverge between nocturnal and diurnal animals those primarily responsible for acute light-induced changes (i.e. activation of sympathetic outflow to the adrenals) are retained. Indeed, since light increases neural activity in the human SCN (McGlashan *et al.*, 2018), just as it does in rodents, such an

arrangement could account for the more commonly observed light-induced increases, rather than decreases, in human CORT levels.

Daily control of the hypothalamic-pituitary-gonadal axis

Reproductive function, particularly in females, is a highly rhythmic process with appropriate timing crucial to a successful outcome, from maximising chances of fertilisation to ensuring the long-term survival of the offspring. Accordingly there has been extensive research on both the relevant mechanisms of circadian control (Simonneaux and Bahougne, 2015, Evans and Anderson, 2018) and with respect to photoperiodic seasonal regulation (Dardente et al., 2019). For reasons of space, below we focus on the known circuitry by which SCN and light-dependent signals can most directly modulate the hypothalamic-pituitary-gonadal (HPG) axis.

The key drivers of the HPG axis are the GnRH neurons in the pre-optic area of the hypothalamus. GnRH, secreted into the portal circulation, then acts in the anterior pituitary to trigger systemic release of luteinising hormone (LH) and follicle stimulating hormone (FSH) which in turn stimulate gonadal hormone secretion (Herbison, 2016). Rodent studies indicate that the SCN sends direct outputs to GnRH neurons, a projection which, at least in part, originates with VIP expressing cells (Van der Beek *et al.*, 1997, van der Beek *et al.*, 1993, Mahoney and Smale, 2005a, Ward *et al.*, 2009). VIP then excites GnRH neurons, providing a potential route by which HPG axis activity may be controlled according to time of day (Piet *et al.*, 2016). SCN VIP cells may also indirectly excite GnRH neurons by supressing the activity of upstream inhibitory neurons in the DMH expressing RFamide-related peptide 3 (Russo *et al.*, 2015). Similarly, AVP expressing SCN neurons provide a further indirect source of circadian control by exciting kisspeptin neurons in the anteroventral periventricular nuclei which, in turn, powerfully stimulate GnRH neurons (Vida *et al.*, 2010, Williams *et al.*, 2011, Simonneaux and Bahougne, 2015).

The mechanisms described above appear to converge to provide circadian regulation of female reproductive function (Fig. 6). In rodents, a surge in LH release, critical for triggering ovulation, is timed to occur towards the end of the day; this requires SCN-dependent circadian timing signals co-incident with high levels of estradiol, indicative of ovarian follicle maturation (Brown-Grant and Raisman, 1977, Wiegand *et al.*, 1980, Lehman et al., 1987, Meyer-Bernstein et al., 1999). Initial studies indicated that a reduction in either VIP or AVP signalling could attenuate this LH surge (Harney *et al.*, 1996, van der Beek *et al.*, 1999, Funabashi *et al.*, 1999). Subsequent studies now suggest that AVP-expressing SCN cells, acting via kisspeptin neurons, are likely the primary drivers of the timing of the pre-ovulatory LH surge and its gating by estradiol (Robertson *et al.*, 2009, Smarr *et al.*, 2012).

In line with the above, appropriately timed (late day) administration of AVP appears sufficient to produce the LH surge in estradiol-treated ovariectomised rats (Palm *et al.*, 1999, Palm *et al.*, 2001). By contrast the influence of VIP on the proestrous LH surge appear more modulatory in nature (Sun *et al.*, 2012). These time-dependent effects of exogenous peptide application further indicate that rhythms in SCN output cannot be the sole factors dictating the circadian timing of LH release. Certainly, GnRH neurons themselves possess an intrinsic molecular clock (Hickok and Tischkau, 2010) and exhibit circadian variation in their response to key inputs such as Kisspeptin and VIP (Christian and Moenter, 2008, Williams et al., 2011),

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as may other key upstream cell types highlighted above (Russo et al., 2015, Simonneaux and Bahougne, 2015).

In summary, the circuitry underlying circadian control of the HPG axis is complex, with multiple pathways that converge to regulate daily rhythms in GnRH neurons. In nocturnal rodents at proestrous this results in an LH surge around dusk, ensuring ovulation occurs during their active phase, when mating is likely. Although far less studied, broadly similar circuits in male animals presumably confer a corresponding daily rhythmicity in the HPG axis (e.g. (Taya and Igarashi, 1974, Roman *et al.*, 2003)), ensuring reproductive function is appropriately aligned in both sexes to maximise successful procreation (Sakai and Endo, 1988). Of course it is also important to note here that, as discussed above for CORT, the timing of rhythms in HPG axis activity will be different in diurnal species (Baumgartner *et al.*, 1993, Mahoney *et al.*, 2004, Caufriez *et al.*, 2018). For example, in female *Arvincanthis*, GnRH neuronal activity and LH secretion is maximal just prior to dawn (Mahoney et al., 2004). Further, both male and female *Arvincanthis* display correspondingly enhanced sexual behaviour at this time, as opposed to just after dusk as in nocturnal rodents (Mahoney and Smale, 2005b). The mechanisms responsible for this phase inversion are currently unclear but are expected to lie in difference in the intermediary circuitry linking the SCN to GnRH neurons rather than any major difference in the timing of SCN output.

Beyond the circadian control outlined above, it is also important to consider other influences of the light environment on HPG axis function. One such example, which is critical for the seasonal breeding adaptions shown by many mammals, is day-length. Variations in day-length can evoke rapid changes in reproductive status that involve the same circuitry as that enaged by the circadian clock (Angelopoulou *et al.*, 2019). Importantly, however, in this case the primary source of photoperiodic information is rather indirect, coming via a change in duration of melatonin secretion (Wood and Loudon, 2018). Nonetheless, given that many SCN neurons are acutely modulated by light, including the VIP cells (Jones *et al.*, 2018) which have known roles in regulating GnRH neuronal activity, one might wonder whether there are also more direct sources of light-dependent control.

Although the possibility of acute effects of light of this nature not been studied in detail, a previous report does indicate that putative GnRH neurons in the monkey hypothalamus exhibit acute light dependent increases in activity (O'Byrne *et al.*, 1993). There are several potential origins for this although, interestingly, direct retinal projections to GnRH neurons have been reported in monkeys (Abizaid *et al.*, 2004). Further, there have been a few reports that acute light exposure can induce very rapid increases in circulating FSH, and perhaps also LH, levels in human females (Miyauchi *et al.*, 1990, Miyauchi *et al.*, 1991, Danilenko and Sergeeva, 2015). There is also data supporting the existence of very rapid light-dependent changes in HPG activity in rodents, although the data are conflicting: bright light reportedly enhances the pre-ovulatory LH surge in female rats (Walker and Jimenez, 1984) but supresses this in mice (Bronson and Vom Saal, 1979). One possible explanation for such discrepancies relates to a differential contribution of melatonin to the observed responses. Hence, the mouse strain used above (CF-1), like many other lab strains (but unlike rats), is expected to lack significant melatonin production (Kasahara *et al.*, 2010).

Daily control of other anterior pituitary hormones

Other anterior pituitary hormones associated with control of reproductive function are also under strong circadian regulation. Prolactin secretion is under tonic inhibitory control from neuroendocrine dopaminergic neurons, found in several hypothalamic sites which are directly targeted by SCN efferent projections (Horvath, 1997). Further studies have since revealed that SCN projections to neuroendocrine dopaminergic cells in both nocturnal and diurnal rodents arise, at least in part, with VIP expressing cells (Gerhold *et al.*, 2001, Mahoney *et al.*, 2007). In addition, however, VIP cells in rat SCN also appear to provide input to another neurosecretory cell type capable of stimulating prolactin secretion - oxytocin neurons of the PVN (Egli *et al.*, 2004). The existence of this additional projection therefore provides a route by which VIP cell activity could bi-directionally control prolactin secretion.

In line with the circuit complexity highlighted above, the timing and diurnal pattern of prolactin secretion seems to exhibit significant flexibility according to species, sex, reproductive status, environmental conditions etc. (Sinha *et al.*, 1975, Meier and Cincotta, 1996, Rietema *et al.*, 2015, Roelfsema and Pijl, 2012, van Kerkhof *et al.*, 2015, Cano *et al.*, 2008, Claustrat *et al.*, 2008, Dubey *et al.*, 1983). Nonetheless, the studies listed above (which include data from sheep, monkeys, humans and male nocturnal rodents) typically reveal higher levels of circulating prolactin during the night. While the mechanisms responsible for controlling the timing of the prolactin rhythms are generally not well understood, the presence of a nocturnal peak could be considered to imply a net inhibitory impact of (presumably day-active; (Jones *et al.*, 2015)) SCN VIP cells.

To date, however, direct mechanistic investigations of SCN contributions to regulating prolactin secretion, which have focused on female rodents, seem to suggest the opposite. Hence, lesion studies provide evidence that neural output form the SCN drives a reduction in dopamine outflow to the median eminence which, in turn, triggers a late-day surge in prolactin release under conditions mimicking proestrous (Mai *et al.*, 1994). Knockdown of VIP expression in SCN does not seem to influence this apparent stimulatory effect of SCN output on prolactin release (Harney et al., 1996). This does not necessarily rule out an involvement of VIP cells, however, as this cell population could would still be capable of proving GABA-mediated inhibition of the relevant dopaminergic neurons. In addition, cervical stimulation (or mating) induces a biphasic rhythm in prolactin secretion in female rats, and here VIP knockdown does disrupt the late-day (but not morning) peak (Egli et al., 2004). Further, in this paradigm, both morning and evening peaks in prolactin secretion are abolished by SCN-specific clock gene knockdowns (Poletini *et al.*, 2010). In sum, then, these data suggest a net stimulatory role of SCN output on prolactin secretion which involves more than one population of neurons, at least one of which produces VIP.

As discussed above for GnRH neurons, beyond circadian and indirect seasonal related changes (Dardente et al., 2019), there are also several ways that the light environment could acutely regulate prolactin secretion. Indeed, such information could come via light-driven increases in VIP cells activity, via projections to neuroendocrine dopaminergic neurons from visual thalamic neurons (Horvath, 1998) and/or via direct retinal projections to this population of cells (Abizaid et al., 2004). Functional evidence for acute light-driven modulation in prolactin secretion is scant, however. There have been a few reports that bright illumination supresses the nocturnal increase in prolactin secretion in human females (Bispink *et al.*, 1990, Miyauchi et al., 1991, Okatani and Sagara, 1993), however other studies have reported no effects

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(Byerley *et al.*, 1988, Miyauchi et al., 1990, McIntyre *et al.*, 1992, Danilenko and Sergeeva, 2015). In sum, while there is evidence consistent with the idea that light may acutely supress prolactin via direct or indirect excitation of dopaminergic neuroendocrine neurons, the magnitude of the effect is likely modest.

The SCN also exerts direct daily control over another key mediator of seasonal adaptations, thyroid hormone signalling. Hence, in rat, SCN cells are known to innervate TRH neurons in the PVN which drive thyroid stimulating hormone (TSH) release from the anterior pituitary (Kalsbeek et al., 2000a). Interestingly, this study also provides evidence that these TRH neurons also form part of the multisynaptic pathway controlling autonomic input to the thyroid gland, providing a potential mechanism for adjusting sensitivity to circulating TSH.

As with prolactin, diurnal patterns of TSH appears to vary depending on sex, species and/or gender studied. However, nocturnal rodents typically display elevated TSH during the early-mid day (Fukuda *et al.*, 1975, Rookh *et al.*, 1979, Wong *et al.*, 1983), while in humans TSH levels are elevated in the early-mid night (Hirschfeld *et al.*, 1996, Leproult *et al.*, 1997, van Kerkhof et al., 2015). In rats, SCN lesions result in significant changes in the diurnal pattern of circulating TSH and thyroid hormone (Abe *et al.*, 1979, Kalsbeek et al., 2000a), confirming a role for the central clock in regulating these. However, there are also potential effects of sleep on the observed diurnal patterns, with sleep known to supress nocturnal TSH levels in humans (Baumgartner et al., 1993, Allan and Czeisler, 1994). Further, nocturnal light exposure has been reported to increase human TSH levels (Hirschfeld et al., 1996), although other studies have reported no effect of light on circulating TSH (Leproult et al., 2001, Leproult et al., 1997). In sum then, daily patterns of thyroid function are likely a composite of comparatively direct circadian influences as well as behaviourally generated influences (sleep and/or light exposure) which are indirectly influenced by the circadian clock.

Conclusions

As highlighted throughout this review, the light environment has profound and wide-ranging impacts on neuroendocrine function. The existence of multiple pathways by which circadian and/or visual signals can directly influence most of the body's major hormonal systems (including effects due to interactions with other hormonal systems or relevant behavioural state changes) makes unpicking the key underlying mechanisms challenging. Nonetheless we currently have a reasonable understanding of the primary pathways responsible for circadian control of many key neuroendocrine signals in rodents. In some cases (e.g. melatonin) this understanding is directly applicable also to humans and other diurnal animals. In most other cases however there is significant uncertainty as to how differences in the underlying circuity are used to adjust the phase of hormonal rhythms to match a diurnal rather than nocturnal lifestyle.

Perhaps the most significant gap in our current knowledge, however, relates to more direct effects of light on neuroendocrine function. Understanding of sensory control of the circadian system itself has advanced substantially in the past 20 years (Brown, 2016). In parallel, significant progress is being made understanding the sensory control of melatonin synthesis, highlighting a dominant role for melanopsin-based signals (Najjar et al., 2014, Prayag et al., 2019). Even here, though, the contribution of other sorts of sensory information (e.g. luminance or colour signals) is uncertain. Moreover, there is little to no clear information

regarding sensory influences on other hormonal signals. Thus, despite evidence for light dependent changes (e.g. in CORT) and identified circuity that could support such effects, existing studies have not attempted to dissect the photoreceptive signals involved in detail.

Recent advances in the sophistication of the experimental stimuli used to probe such responses, which allow for selective modulation of specific photoreceptor classes (Walmsley et al., 2015, Hayter and Brown, 2018, Allen *et al.*, 2018), now offer a clear path to answering current unknowns in this area. Indeed, when used in combination with the latest intersectional genetics tools for circuit mapping (e.g. (Jones et al., 2015, Hanna *et al.*, 2017)), achieving a detailed understanding of the circadian/sensory control at each stage of the key neuroendocrine control pathways is now within reach.

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Declaration of interest

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

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Figure Legends

Figure 1. Pathways for circadian and light dependent changes in neuroendocrine function. A light-regulated clock in the suprachiasmatic nucleus (SCN) provides circadian timing information to neurosecretory and pre-autonomic neurons in other hypothalamic regions to provide daily control of neuroendocrine function. Light may also acutely modulate neuroendocrine function due to rapid changes in the activity of retinorecipient SCN neurons and/or via direct retinal projections to other hypothalamic regions. Circadian and light dependent changes in behavioural state (e.g. sleep/rest; feed/fast) can also indirectly influence neuroendocrine function, as can feedback/crosstalk within and between specific neuroendocrine systems.

Figure 2. Retinal circuitry supporting effects of light on neuroendocrine function. (A) Schematic of important retinal circuits that supply intrinsically photosensitive retinal ganglion cells (ipRGCs). In addition to intrinsic melanopsin-based phototransduction, ipRGCs receive excitatory cone input via ON bipolar cells and excitatory rod input via rod bipolar cells that couple to the cone bipolars via gap junctions. Widefield amacrine cell connections provide inhibitory input from other cone bipolar cells, potentially allowing from chromatic responses (Stabio *et al.* 2018). (**B**) Relationship between light intensity and ipRGC firing, indicating photoreceptive systems that contribute under each condition. Note that natural variations in spectral composition during twilight (indicated by coloured bar) are detectable to cones and can modulate the intensity-dependent firing of ipRGCs.

Figure 3. Heterogeneity in central clock neurons and their response to light. (A) The suprachiasmatic nucleus (SCN) contains two interconnected subregions each with a variety of neuropeptidergic cell types which differ with respect to retinal input and efferent connectivity. (**B**) Circadian activity patterns in SCN neurons exhibit a broad distribution of phasing, centered on the middle of the external day, providing a robust population-level diurnal output but allowing individual neurons to convey distinct timing signals. (**C**) SCN neurons exhibit a variety of different visual response properties as revealed by selective stimulation of melanopsin or cones. Most display melanopsin-dependent responses but differ in cone-based responses; top-bottom: response to luminance contrast, blue-ON colour opponent, yellow-On colour opponent, weak cone responses, visually unresponsive (based on Walmsley *et al.* 2015).

Figure 4. Pathway for circadian and light-dependent changes in pineal melatonin. A polysynaptic pathway originating with intrinsically photosensitive retinal ganglion cell projections to the suprachiasmatic Nucleus (SCN) provides circadian and light dependent control of melatonin synthesis and release. SCN neurons inhibit pre-autonomic paraventricular nucleus (PVN) neurons which regulate sympathetic innervation of the pineal, resulting in an inverse relationship between SCN activity and melatonin secretion. By stimulating SCN activity during the circadian night, light can acutely inhibit melatonin secretion. Under diurnal conditions, a combination of circadian and light-dependent regulation modulates the daily duration of melatonin secretion, providing information about day-length.

Figure 5. Circuitry underlying circadian and light-dependent control of the rodent hypothalamic-pituitary-adrenal (HPA) axis. HPA axis control involves neurosectretory (denoted C) and autonomic pathways (deonted A). Circadian output from arginine vasopressin (AVP) cells of the suprachiasmatic nucleus (SCN), acting via inhibitory interneurons in the

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Dorsomedial Hypothalamus, inhibits corticotrophin releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) to drive a daily rhythm in adrenocorticotrophin hormone (ACTH) secretion from anterior pituitary corticotrophs. Circadian and light-dependent signals (presumed to originate primarily with SCN VIP cells) stimulate pre-autonomic PVN neurons which project via the intermediolateral spinal cord (IML) to the adrenals to modulate sensitivity to circulating ACTH. AVP cells may also directly innervate CRH and/or preautonomic PVN neurons.

Figure 6. Circuitry underlying circadian and light dependent changes in the HPG axis of female rodents. Circadian signals from arginine vasopressin (AVP) cells of suprachiasmatic nucleus (SCN) drive kisspeptin neurons in the anteroventral periventricular nuclei which potently stimulate gonadotrophin releasing hormone (GnRH) neurons in the preoptic area in the presence of estradiol. Vasoactive intestinal polypeptide (VIP) cells, potentially relaying circadian and light-dependent signals, directly innervate GnRH neurons and RFamide-related peptide 3 (RFRP3) expressing cells which provide inhibitory input to GnRH cells. GnRH cells also appear to receive some direct retinal input and possess an intrinsic molecular clock which regulates their response to other inputs. GnRH neurons then signal to pituitary gonadotrophs to drive luteinising hormone (LH) and follicle stimulating hormone (FSH) release.

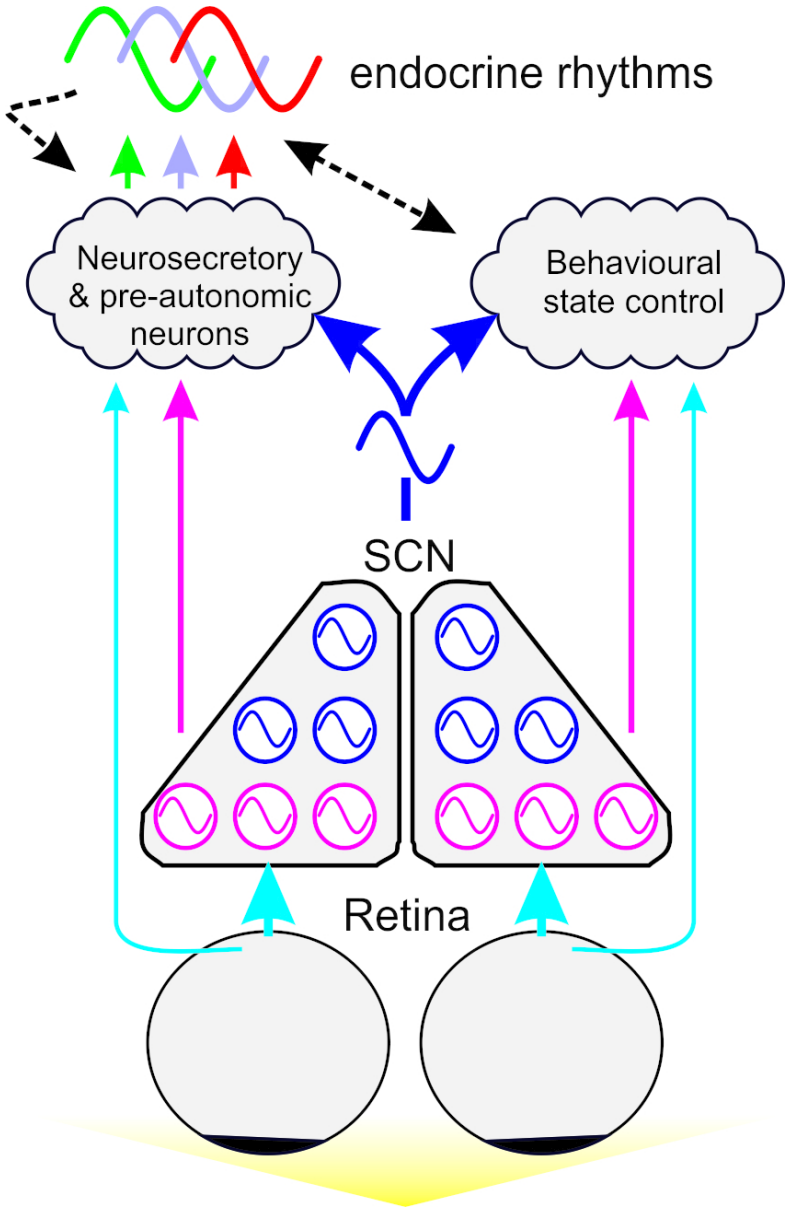

Figure 1. Pathways for circadian and light dependent changes in neuroendocrine function. A light-regulated clock in the suprachiasmatic nucleus (SCN) provides circadian timing information to neurosecretory and pre-autonomic neurons in other hypothalamic regions to provide daily control of neuroendocrine function. Light may also acutely modulate neuroendocrine function due to rapid changes in the activity of retinorecipient SCN neurons and/or via direct retinal projections to other hypothalamic regions. Circadian and light dependent changes in behavioural state (e.g. sleep/rest; feed/fast) can also indirectly influence neuroendocrine function, as can feedback/crosstalk within and between specific neuroendocrine systems.

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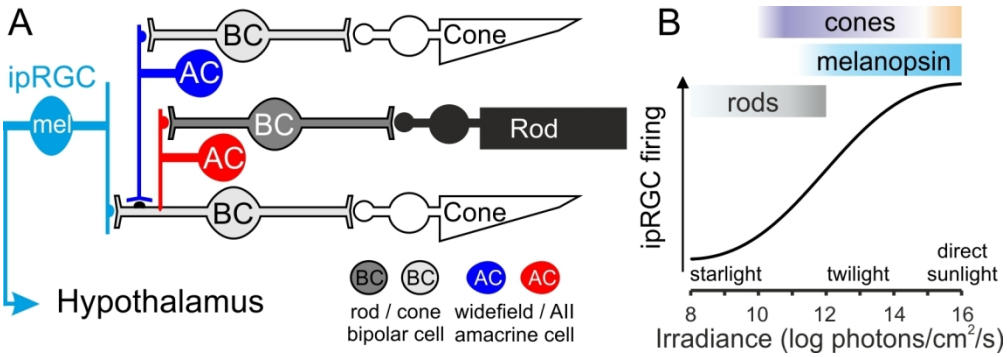

Figure 2. Retinal circuitry supporting effects of light on neuroendocrine function. (A) Schematic of important retinal circuits that supply intrinsically photosensitive retinal ganglion cells (ipRGCs). In addition to intrinsic melanopsin-based phototransduction, ipRGCs receive excitatory cone input via ON bipolar cells and excitatory rod input via rod bipolar cells that couple to the cone bipolars via gap junctions. Widefield amacrine cell connections provide inhibitory input from other cone bipolar cells, potentially allowing from chromatic responses (Stabio et al. 2018). (B) Relationship between light intensity and ipRGC firing, indicating photoreceptive systems that contribute under each condition. Note that natural variations in spectral composition during twilight (indicated by coloured bar) are detectable to cones and can modulate the intensity-dependent firing of ipRGCs.

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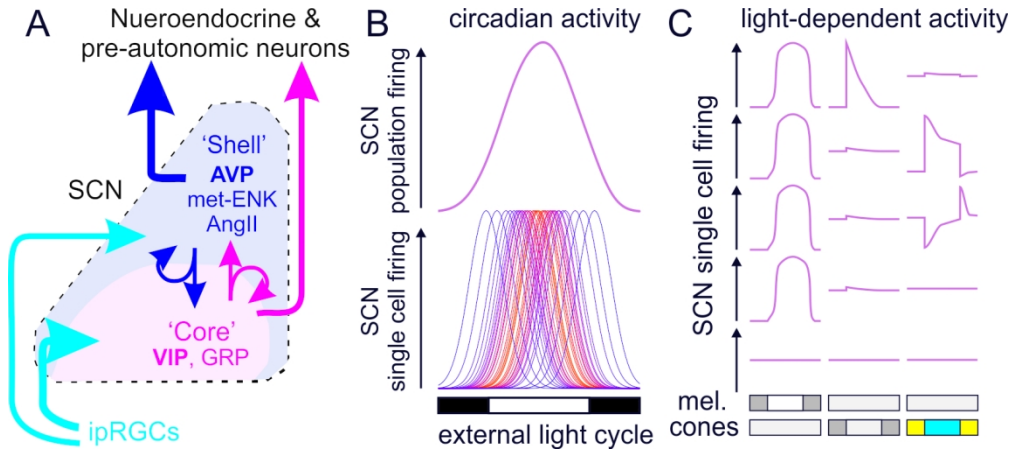

Figure 3. Heterogeneity in central clock neurons and their response to light. (A) The suprachiasmatic nucleus (SCN) contains two interconnected subregions each with a variety of neuropeptidergic cell types which differ with respect to retinal input and efferent connectivity. (B) Circadian activity patterns in SCN neurons exhibit a broad distribution of phasing, centered on the middle of the external day, providing a robust population-level diurnal output but allowing individual neurons to convey distinct timing signals. (C) SCN neurons exhibit a variety of different visual response properties as revealed by selective stimulation of melanopsin or cones. Most display melanopsin-dependent responses but differ in cone-based responses; top-bottom: response to luminance contrast, blue-ON colour opponent, yellow-On colour opponent, weak cone responses, visually unresponsive (based on Walmsley et al. 2015).

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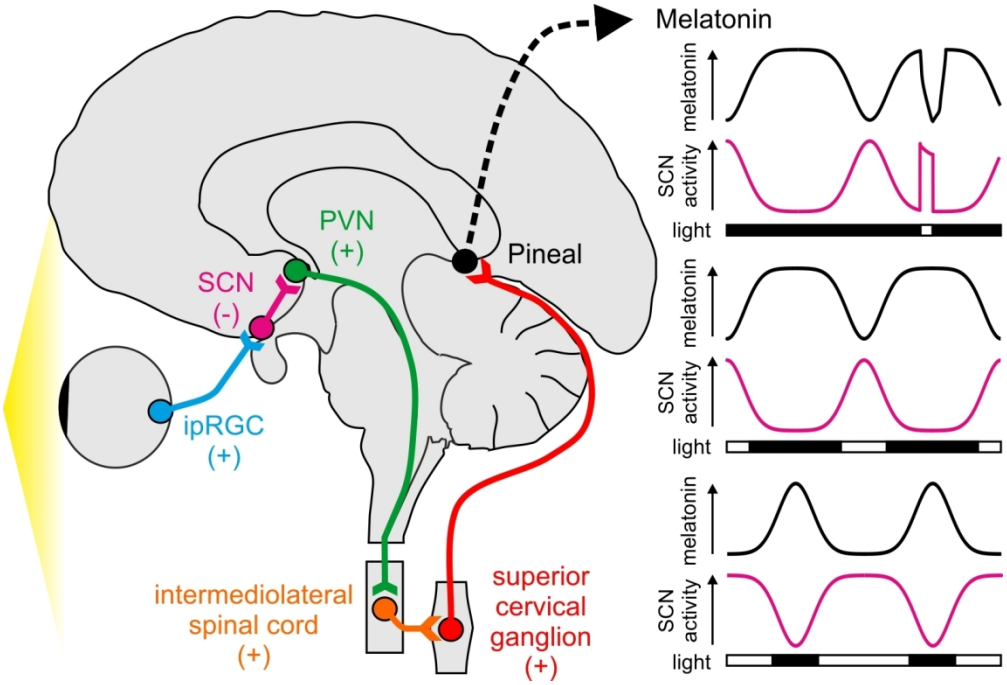

Figure 4. Pathway for circadian and light-dependent changes in pineal melatonin. A polysynaptic pathway originating with intrinsically photosensitive retinal ganglion cell projections to the suprachiasmatic Nucleus (SCN) provides circadian and light dependent control of melatonin synthesis and release. SCN neurons inhibit pre-autonomic paraventricular nucleus (PVN) neurons which regulate sympathetic innervation of the pineal, resulting in an inverse relationship between SCN activity and melatonin secretion. By stimulating SCN activity during the circadian night, light can acutely inhibit melatonin secretion. Under diurnal conditions, a combination of circadian and light-dependent regulation modulates the daily duration of melatonin secretion, providing information about day-length.

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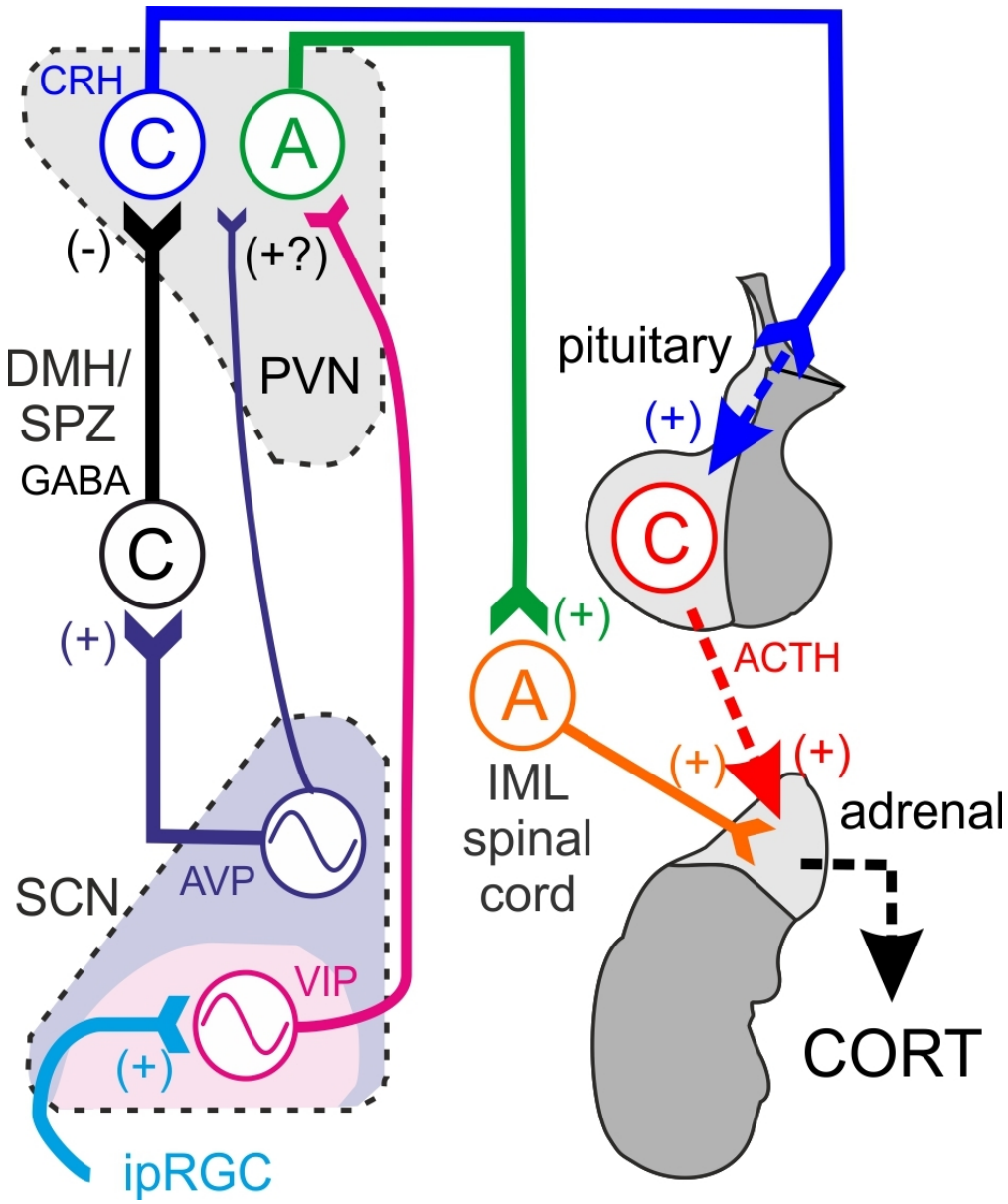

Figure 5. Circuitry underlying circadian and light-dependent control of the rodent hypothalamic-pituitary-adrenal (HPA) axis. HPA axis control involves neurosectretory (denoted C) and autonomic pathways (deonted A). Circadian output from arginine vasopressin (AVP) cells of the suprachiasmatic nucleus (SCN), acting via inhibitory interneurons in the Dorsomedial Hypothalamus, inhibits corticotrophin releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) to drive a daily rhythm in adrenocorticotrophin hormone (ACTH) secretion from anterior pituitary corticotrophs. Circadian and light-dependent signals (presumed to originate primarily with SCN VIP cells) stimulate pre-autonomic PVN neurons which project via the intermediolateral spinal cord (IML) to the adrenals to modulate sensitivity to circulating ACTH. AVP cells may also directly innervate CRH and/or preautonomic PVN neurons.

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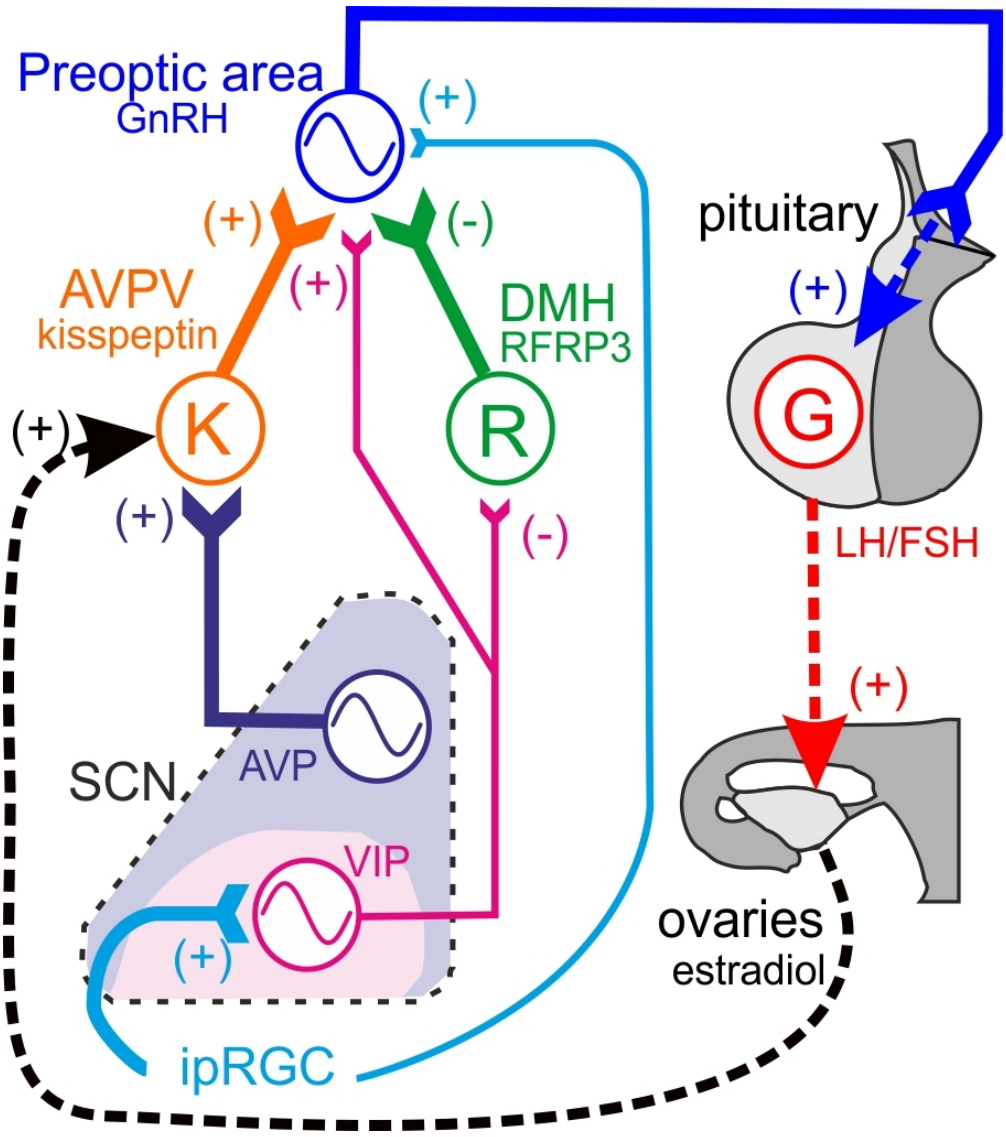

Figure 6. Circuitry underlying circadian and light dependent changes in the HPG axis of female rodents. Circadian signals from arginine vasopressin (AVP) cells of suprachiasmatic nucleus (SCN) drive kisspeptin neurons in the anteroventral periventricular nuclei which potently stimulate gonadotrophin releasing hormone (GnRH) neurons in the preoptic area in the presence of estradiol. Vasoactive intestinal polypeptide (VIP) cells, potentially relaying circadian and light-dependent signals, directly innervate GnRH neurons and RFamide-related peptide 3 (RFRP3) expressing cells which provide inhibitory input to GnRH cells. GnRH cells also appear to receive some direct retinal input and possess an intrinsic molecular clock which regulates their response to other inputs. GnRH neurons then signal to pituitary gonadotrophs to drive luteinising hormone (LH) and follicle stimulating hormone (FSH) release.

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