60 YEARS OF NEUROENDOCRINOLOGY

Regulation of mammalian neuroendocrine physiology and rhythms by melatonin

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Abstract

The isolation of melatonin was first reported in 1958. Since the demonstration that pineal melatonin synthesis reflects both daily and seasonal time, melatonin has become a key element of chronobiology research. In mammals, pineal melatonin is essential for transducing day-length information into seasonal physiological responses. Due to its lipophilic nature, melatonin is able to cross the placenta and is believed to regulate multiple aspects of perinatal physiology. The endogenous daily melatonin rhythm is also likely to play a role in the maintenance of synchrony between circadian clocks throughout the adult body. Pharmacological doses of melatonin are effective in resetting circadian rhythms if taken at an appropriate time of day, and can acutely regulate factors such as body temperature and alertness, especially when taken during the day. Despite the extensive literature on melatonin physiology, some key questions remain unanswered. In particular, the amplitude of melatonin rhythms has been recently associated with diseases such as type 2 diabetes mellitus but understanding of the physiological significance of melatonin rhythm amplitude remains poorly understood.

Key Words
- pineal
- pars tuberalis
- pars distalis
- development
- reproduction
- prolactin
- thyroid
- deiodinase
- circadian rhythm
- clock gene
- amplitude

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Melatonin and the photoneuroendocrine system

Overview of melatonin's discovery

The discovery of melatonin was made by Lerner *et al.* (1958), coincidently only a few years after publication of Harris' monograph, Neural Control of the Pituitary Gland (Harris 1955), which is often considered to have established neuroendocrinology as a discipline and is celebrated in this special issue of the journal. Lerner was seeking to identify the molecule(s) in bovine pineal glands known to cause blanching of amphibian skin. This work led to isolation of a factor, termed melatonin, which causes potent aggregation of melanin granules in frog melanocytes (Lerner *et al.* 1958). Shortly afterwards, the chemical structure of melatonin was revealed as N-acetyl-5-methoxytryptamine (Lerner *et al.* 1959). From its origins in a dermatology laboratory, melatonin has become a key molecule in the field of chronobiology. As described in this review, melatonin provides an extremely robust endocrine signal of both circadian time and day-length, enabling it to influence both daily and seasonal rhythms in many species. Melatonin is synthesised by multiple tissues in the body, but the pineal gland is the major

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contributor to circulating melatonin concentration, as pinealectomy abolishes detectable melatonin in the blood (Lewy *et al*. 1980*a*).

Circadian rhythmicity of pineal melatonin synthesis

Concentrations of melatonin in the blood exhibit a pronounced circadian rhythm, with elevated levels during the biological night in all species. The primary driver of melatonin rhythmicity is the endogenous circadian system, as daily rhythms of melatonin persist in constant dim light and in the absence of rhythmic environmental cues. In most mammalian species, the circadian rhythm of pineal melatonin synthesis is due to a poly-synaptic pathway linking the pineal gland to the hypothalamic suprachiasmatic nuclei (SCN), which house the master circadian clock in mammals (Moore & Eichler 1972, Stephan & Zucker 1972). The pathway has been mapped by classical lesioning and tracer studies (reviewed in Moore (1996)), together with transneuronal retrograde tracer experiments (Larsen *et al*. 1998, Teclemariam-Mesbah *et al*. 1999). From the SCN, it passes via the paraventricular nuclei, the upper thoracic intermediolateral cell column of the spinal cord and then sympathetic neurones of the superior cervical ganglion, which innervate the pineal. This series of connections linking retina to SCN to pineal gland is sometimes referred to as a photoneuroendocrine system.

The circadian, SCN-driven sympathetic innervation of the pineal gland results in activation of arylalkylamine-N-acetyltransferase (AA-NAT), a key enzyme in the melatonin synthesis pathway (Klein 2007). Noradrenaline released by the sympathetic neurones stimulates cAMP production and AA-NAT activity in pinealocytes via both β1 (Deguchi & Axelrod 1972, Klein & Weller 1973) and α1 (Klein *et al*. 1983, Vanecek *et al*. 1985) adrenoreceptors. In rodents, this leads to high amplitude rhythms in pineal *Aa-nat* mRNA abundance (Borjigin *et al*. 1995, Coon *et al*. 1995) indicating that AA-NAT synthesis is a major mechanism driving the melatonin synthesis rhythm. However melatonin synthesis in all species also involves important post-translational mechanisms such as the stabilisation of AA-NAT protein by interaction with 14-3-3 proteins (Ganguly *et al*. 2001). In comparison to rodents, pineal physiology of ungulate and primate species is believed to primarily utilise post-transcriptional mechanisms, as it exhibits very little daily change in mRNA of *Aa-nat* and other genes known to be rhythmic in the rodent pineal (Coon *et al*. 1995, Privat *et al*. 1999, Johnston *et al*. 2004). Moreover stimulation of bovine pinealocytes with noradrenaline induces AA-NAT activity without any change in *Aa-nat* mRNA expression (Schomerus *et al*. 2000). Further data describing species differences in melatonin synthesis are reviewed elsewhere (Stehle *et al*. 2001).

In addition to being an SCN-driven rhythm, the daily variation in melatonin synthesis is also in part regulated by the ambient light-dark cycle. Light is a powerful synchroniser of SCN rhythms (reviewed in Hughes *et al*. (2015)). Furthermore, exposure to light during the night acutely inhibits melatonin synthesis and secretion in both animal models (Klein & Weller 1972, Illnerova *et al*. 1979) and humans (Lewy *et al*. 1980*b*). The daily rhythm of melatonin concentration is thus the result of complex interplay between endogenous and exogenous factors.

Melatonin as a marker of circadian phase

The timing of the endogenous melatonin rhythm is considered the most reliable marker of SCN clock timing and is used routinely to assess circadian phase in humans. Melatonin can be measured directly in plasma and saliva samples, or indirectly as its urinary metabolite, 6-sulphatoxymelatonin (aMT6s), thus providing circadian phase information in both laboratory and non-laboratory studies (reviewed in Skene & Arendt (2006)). Compared with core body temperature and cortisol rhythms, melatonin is least affected by activity, sleep, meals and stress.

The timing of the rhythm can be measured by estimating the time of melatonin onset, peak or offset (reviewed in Skene & Arendt (2006)). The time of melatonin onset in dim light conditions, the so-called dim light melatonin onset (DLMO; Lewy & Sack 1989), has frequently been used as a marker of circadian phase, although it may be better to measure both melatonin onset and offset as there is some evidence to suggest that these may be shifted differentially (Warman *et al*. 2003). Preferably, however, the whole melatonin profile should be measured to capture both melatonin timing and amplitude. The timing of the melatonin and urinary aMT6s rhythms has provided important information of an individual's circadian phase in numerous studies of circadian desynchrony and has also been used to optimize the timing of light and melatonin in the treatment of circadian rhythm sleep–wake disorders.

Melatonin as an endocrine calendar

The 24-h melatonin signal not only represents endogenous circadian time but also encodes seasonal information.

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Specifically, the duration of elevated melatonin concentration is proportional to duration of the night and thus dependent upon the prevailing photoperiod (reviewed in Reiter (1993)). This photoperiodic regulation of melatonin signal duration is a consequence of adaptation of SCN physiology. Day-length is encoded in multiple SCN rhythms, including gene expression, electrical activity and gating of sensitivity to input stimuli as reviewed elsewhere (Johnston 2005, Coomans *et al.* 2015). Altered neuronal output from the SCN then drives melatonin signal duration via the SCN-pineal poly-synaptic pathway as described above.

The ability of melatonin to provide an endocrine representation of photoperiod is an essential component of the seasonal biology of many species. Removal of the pineal gland has long been known to block the ability of photoperiod to regulate the seasonal physiology of mammals. However there was debate in the literature as to what element(s) of the melatonin signal actually carried photoperiodic information. Early studies of intact hamsters revealed an ability of melatonin injections to induce short photoperiod-like physiology, but only when given at certain times of the day (Tamarkin *et al.* 1976, 1977). Possible explanations for these data included rhythmic sensitivity to melatonin and extension of the endogenous melatonin signal duration by the injections. A series of elegant timed infusion studies conducted by multiple laboratories using pinealectomised animals later revealed that duration is likely to be the key feature of the melatonin rhythm that regulates photoperiodic changes in physiology (reviewed in Bartness *et al.* (1993)). The contrast between short duration signals in the summer and long duration winter signals is both necessary and sufficient to drive subsequent seasonal rhythms in diverse processes such as reproduction, pelage, metabolism, and immune function (Goldman 2001, Stevenson & Prendergast 2015).

Melatonin receptors

Endogenous melatonin acts through activation of membrane bound, high affinity, G-protein coupled receptors. Early studies using the radioligand 2-[^{125}I]iodomelatonin identified and quantified high-affinity melatonin receptors in numerous vertebrate species (Dubocovich 1995, Reppert & Weaver 1995, Vanecek 1988*a*). Subsequent molecular cloning identified two melatonin receptors, Mel1a (MT1) and Mel1b (MT2) in mammals (Reppert *et al.* 1994, 1995*a*) and an additional melatonin receptor, Mel1c, in birds (Reppert *et al.* 1995*b*). The MT2 receptor was cloned from humans (362 amino acids) and is 60% identical to the human MT1 receptor at the amino acid level (350 amino acids). The MT2 receptor is preferentially expressed in the human retina and selected brain regions, notably the hippocampus. The expressed recombinant MT2 receptor exhibits similar ligand binding characteristics and pharmacology to the MT1 receptor (Kd $<$200 pM; specificity 2-iodomelatonin $>$melatonin $\geq$6-chloromelatonin $>$N-acetylserotonin $>>$serotonin) and is also coupled to G_i resulting in inhibition of adenylate cyclase, cAMP concentration and downstream signal transduction pathways (Reppert 1997).

There is a high density of melatonin receptor expression in neuroendocrine tissues, including the hypothalamic SCN, pituitary pars tuberalis (PT) and developing gonadotroph cells. Melatonin receptors have also been detected elsewhere, including the adrenal gland (MT1), arteries and heart (MT1, MT2), lung (MT1, MT2), liver (MT1, MT2), kidney (MT1), small intestine (MT2), skin (MT1, MT2), and in T and B lymphocytes (MT1) (reviewed in Zawilska *et al.* (2009)). However the physiological function of melatonin is not well understood in many of these tissues. Notable examples of melatonin's regulation of endocrine function include regulation of metabolic physiology, such as insulin secretion and glucose homeostasis (Peschke 2008, Karamitri *et al.* 2013). This review, however, will focus on neuroendocrine examples, primarily via its action in the hypothalamus and pituitary gland.

Circadian actions of endogenous melatonin in adults

The MT1 receptor is strongly expressed in the SCN, which is considered a major site of melatonin action. Early studies using mice with targeted disruption of the Mel1a (MT1) receptor revealed that this receptor was necessary for the acute inhibitory action of melatonin on SCN neuronal firing (Liu *et al.* 1997). However, phase shifts by melatonin were still evident in these MT1 deficient mice (Liu *et al.* 1997). Subsequent transgenic studies (von Gall *et al.* 2002*b*, Jin *et al.* 2003) and pharmacological studies showing blockade of melatonin-induced phase shifts by MT2 antagonists (Dubocovich *et al.* 1998, Hunt *et al.* 2001) suggest MT2 receptor involvement in melatonin's phase shifting action.

In addition to its effects in the SCN, melatonin's robust rhythmicity in the circulation makes it an attractive candidate molecule involved in the synchronisation of circadian clocks throughout the body. This issue

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has been discussed in detail by others (Stehle *et al*. 2003, Pevet *et al*. 2006).

Regulation of seasonal physiology via the pituitary pars tuberalis (PT)

Aside from the SCN, the pituitary gland is the best studied melatonin target tissue. In adult mammals, the dominant pituitary site of melatonin action is the PT, a thin layer of the anterior pituitary that surrounds the pituitary stalk and extends rostrally along the ventral surface of the median eminence (reviewed in Wittkowski *et al*. (1999)). Co-localisation studies have revealed expression of MT1 receptors in thyroid stimulating hormone (TSH)-positive cells of the PT (Klosen *et al*. 2002, Dardente *et al*. 2003*a*). These cells are often referred to as PT-specific thyrotrophs. Despite their expression of TSH, they lack cellular components associated with the primary population of thyrotroph cells in the pars distalis of the anterior pituitary (Bockmann *et al*. 1997). It is now believed that melatonin signal duration drives the photoperiodic control over multiple aspects of neuroendocrine physiology, including the lactotrophic and reproductive axes, via the PT in adult mammals.

Photoperiodic regulation of prolactin secretion

In many seasonally breeding species, the lactotrophic axis exhibits robust annual cycles with increased prolactin secretion during the spring and summer months, irrespective of the timing of the breeding season. Compelling *in vivo* evidence for an intra-pituitary mechanism regulating photoperiodic prolactin rhythm came from the hypothalamo-pituitary disconnected (HPD) ram model. The HPD ram lacks neuronal connections between the hypothalamus and pituitary gland, but has intact pituitary vasculature (Clarke *et al*. 1983). Despite this lack of neuronal connection between hypothalamus and pituitary, alternate summer and winter photoperiods are able to drive appropriate annual cycles of plasma prolactin concentration (Lincoln & Clarke 1994).

Studies of pituitary melatonin receptor expression revealed a lack of melatonin receptors on lactotroph cells, implying an indirect mechanism of melatonin on prolactin secretion. The importance of the PT in the seasonal regulation of prolactin secretion was first demonstrated by the fact that PT-conditioned medium stimulates prolactin secretion from pituitary pars distalis cell cultures (Hazlerigg *et al*. 1996, Morgan *et al*. 1996). It was therefore postulated that the photoperiodic melatonin signal regulates the release of a prolactin secretagogue, termed tuberalin, from the PT. Later evidence indicated that tuberalin secretion is dependent upon photoperiod (Stirland *et al*. 2001) and endogenous seasonal timing mechanisms (Johnston *et al*. 2003*a*, Lincoln *et al*. 2005). Despite strong evidence for the existence of tuberalin, attempts to identify it have not been successful (Lafarque *et al*. 1998, Guerra & Rodriguez 2001, Graham *et al*. 2002). More detailed reviews of this subject can be found elsewhere (Johnston 2004, Dardente 2007, Dupre 2011).

Photoperiodic regulation of reproduction

More recently, the PT has also been implicated in melatonin-driven seasonal reproductive rhythms. Based upon the results from the HPD ram (Lincoln & Clarke 1994) and lesioning studies in seasonally breeding hamsters (Maywood & Hastings 1995), 'a dual site hypothesis' was originally proposed, in which melatonin acted at the PT to regulate seasonal prolactin rhythms, but in the hypothalamus to regulate seasonal reproduction. Despite this supportive evidence, there were also data in conflict with the dual-site hypothesis. For example, some seasonally breeding species had no detectable melatonin receptors within the hypothalamus (Weaver & Reppert 1990).

Data have linked thyroid hormone physiology to seasonality in birds for many years (reviewed in Follett & Nicholls (1984)). A more recent breakthrough in the understanding of seasonal physiology also came from studies of birds, specifically the Japanese quail. This research revealed that photoperiod regulates expression of deiodinase (DIO) enzymes within the hypothalamus to drive seasonal variation in local concentration of tri-iodothyronine (T_3), the most active form of thyroid hormone (Yoshimura *et al*. 2003, Yasuo *et al*. 2005). This model has now been extended to mammals, in which it had been previously demonstrated that thyroid hormone signalling is involved in seasonal rhythms (Vriend 1985, Nicholls *et al*. 1988, Moenter *et al*. 1991, Webster *et al*. 1991). In brief, melatonin action on the PT-specific thyrotroph cells is proposed to regulate release of TSH, which then functions via a retrograde signalling pathway to regulate DIO expression in hypothalamic tanycytes that line the third ventricle (Hanon *et al*. 2008). Increased expression of DIO2 and/or reduced DIO3 in the lengthening photoperiods of spring and summer then increases conversion of thyroxine to T_3. The mechanism to produce locally elevated T_3 concentrations in long photoperiods

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appears to be the same in both long and short-photoperiod breeders (Revel *et al*. 2006, Hanon *et al*. 2008). This therefore suggests that species-specific mechanisms within the hypothalamus regulate seasonal breeding status downstream of T_3 generation. For further detail, readers are referred to recent reviews of this topic (Yoshimura 2013, Dardente *et al*. 2014, Wood & Loudon 2014).

Decoding the durational melatonin signal

Despite recent advances in determining the endocrine mechanisms through which melatonin drives seasonal physiology, the cell signalling mechanisms used to interpret melatonin signal duration are still unclear. To date, evidence suggests that melatonin duration is able to alter sensitisation of intracellular signal transduction pathways and also determine the temporal coincidence of rhythmic gene expression.

Chronic activation of receptors that are negatively coupled to adenylate cyclase (AC) can lead to sensitisation of AC signal transduction pathways (Thomas & Hoffman 1987). Indeed, pre-treatment of Chinese hamster ovary cells expressing human MT1 (Witt-Enderby *et al*. 1998), neonatal rat pituitary cells (Pelisek & Vanecek 2000) and pancreatic INS-1β cells (Kemp *et al*. 2002) with melatonin sensitises subsequent stimulation by forskolin. However it is the PT cell model that has been most used to study sensitisation effects of melatonin, as reviewed in detail by Barrett *et al*. (2003). In the context of understanding the decoding of photoperiodic melatonin signalling, it is not sufficient to identify the presence of sensitisation *per se* in PT cells, but determine whether there are differences in sensitisation between melatonin signal durations encountered in long and short photoperiods. This experiment was performed in ovine pituitary cells that, in many temperate latitudes, would be exposed to melatonin signal duration of ~8 h in a long summer photoperiod and 16 h in a short winter photoperiod. Exposure of ovine PT cells to 16 h of melatonin increases AC sensitivity to stimulants such as forskolin (Hazlerigg *et al*. 1993) and CTX (Barrett *et al*. 2000), in addition to causing a significant increase in basal AC activity (Hazlerigg *et al*. 1993). By contrast, exposure to a melatonin signal of 8-h or less causes less sensitisation (Hazlerigg *et al*. 1993). Altered sensitisation of PT cells by physiologically encountered melatonin signals may therefore contribute to photoperiodic timing mechanisms.

Identification of clock gene expression in the PT (Sun *et al*. 1997) invited speculation that there may be circadian mechanisms within the PT involved in decoding melatonin signals. Initial studies focused on *Period1* (*Per1*), which is known to be sensitive to cAMP-dependent signalling, and revealed a transient increase of expression immediately following the morning decline of melatonin (Morgan *et al*. 1998, von Gall *et al*. 2002*a*). Later work revealed rhythmic expression of mRNA for multiple clocks genes in the ovine PT (Lincoln *et al*. 2002). Of note *Cryptochrome1* (*Cry1*) and *Per1* mRNAs were found to be expressed immediately following the onset and offset of the daily melatonin signal, respectively, in both long and short photoperiod (Lincoln *et al*. 2002). As formation of PER and CRY protein complexes is an important functional step in circadian transcriptional repression, it has been hypothesised that melatonin signal duration may transmit day length information via the differential formation of such protein complexes (Lincoln *et al*. 2003). The demonstration that melatonin onset *per se* induces PT expression of *Cry1* (Dardente *et al*. 2003*b*, Hazlerigg *et al*. 2004), made it one of the first genes reported to be acutely stimulated by melatonin. However, subsequent work revealed that melatonin onset stimulates a range of genes and transcription factor pathways (Dupre *et al*. 2008, Fustin *et al*. 2009, Unfried *et al*. 2010), indicating that a molecular coincidence model need not necessarily be dependent upon clock genes, but could conceivably include acute regulation of multiple genes and their protein products. Direct testing of the coincidence model has not yet been possible to a large degree due to the technical difficulty associated with *in vivo* genetic manipulation in photoperiodic species.

Melatonin signalling in neuroendocrine tissues during early development

Although the PT has proved to be a valuable model tissue for the study of melatonin action in adult animals, progress has been made understanding the physiological actions of melatonin elsewhere in the body at various developmental stages. Melatonin became a focus of research on maternal-foetal signalling, due to its robust circadian rhythm and its lipophilic nature, which allows it to cross the placenta (Reppert *et al*. 1979, Yellon & Longo 1987, Zemdegs *et al*. 1988) and even pass into milk (Reppert & Klein 1978, Illnerova *et al*. 1993). In addition to the following examples, evidence indicates effects of maternal melatonin on foetal and neonatal endocrine physiology outside of the scope of this review, including the regulation of adrenal gland (Torres-Farfan *et al*. 2011) and adipose tissue (Seron-Ferre *et al*. 2014) function.

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Direct regulation of the pituitary pars distalis

The distribution of melatonin receptors is more widespread during embryogenesis than in adulthood, suggesting novel role(s) for melatonin in early development (Davis 1997, Seron-Ferre *et al*. 2012). Although developmental changes in melatonin receptor expression have been reported in neuroendocrine tissues such as the thyroid and nasal epithelium (Rivkees & Reppert 1991, Helliwell & Williams 1994), the pituitary gland is the best studied example.

Initial research in this area demonstrated that melatonin is able to acutely inhibit gonadotrophin-releasing hormone (GnRH)-stimulated gonadotrophin secretion from neonatal rat pituitary cells (Martin & Klein 1976). Developmental loss of melatonin sensitivity in the rat pituitary was then revealed by the gradual decline of this endocrine function over the first 2–3 weeks of postnatal life (Martin & Sattler 1979), together with a parallel postnatal loss of iodo-melatonin binding sites (Vanecek 1988*b*). These developmental changes and the mechanisms of melatonin signalling in gonadotroph cells are reviewed in detail elsewhere (Vanecek 1999).

Mapping of *Mt1* mRNA expression using *in situ* hybridisation histochemistry has allowed more detailed analysis of melatonin sensitivity in the developing rat pituitary. Consistent with iodo-melatonin binding studies, the onset of *Mt1* expression is at embryonic day 15 (Johnston *et al*. 2006). During embryogenesis, *Mt1* is strongly expressed in the PT (or rostral tip) region of the anterior pituitary and extends along the ventral pituitary surface, a region known to house newly differentiated gonadotroph cells (Scully & Rosenfeld 2002). Direct evidence of melatonin receptor expression in gonadotroph cells was then provided by co-localisation of *Mt1* with luteinising hormone beta (LHβ) and alpha glycoprotein subunit (αGSU) mRNA in both the embryonic and neonatal rat pituitary (Johnston *et al*. 2003*b*, Johnston *et al*. 2006). The effects of melatonin on reproductive physiology in early development are therefore likely to be, at least in part, via a direct action on the pituitary gonadotroph cells, in contrast to the mechanisms driving photoperiodic reproduction in adults, as previously described.

Investigation of the molecular mechanisms regulating *Mt1* promoter activity has attempted to identify the mechanisms that drive down-regulation of melatonin receptor expression in developing pituitary gonadotroph cells. Sequencing of the rat *Mt1* promoter (Johnston *et al*. 2003*c*) and subsequent reporter assays (Johnston *et al*. 2003*b*) suggested the presence of a functional *cis*-element for the transcription factor EGR-1 proximal to the *Mt1* transcription start site. Expression of EGR-1 in gonadotroph cells is induced by GnRH and is a molecular component through which GnRH stimulates LHβ synthesis (Dorn *et al*. 1999, Tremblay & Drouin 1999). It was therefore hypothesised that, around late embryogenesis in rodents, the onset of pulsatile GnRH secretion from the hypothalamus induces EGR-1 expression to simultaneously stimulate *Lhβ* and inhibit *Mt1* transcription. The hypothesis received support from analysis of the *hypogonadal* mouse, which is unable to synthesise GnRH and exhibits a fourfold increase in pituitary *Mt1* mRNA compared to wild type littermates (Johnston *et al*. 2003*b*). Further support came from *in vitro* experiments, which have shown that endogenous *Mt1* mRNA expression is up-regulated by a GnRH receptor antagonist in GT1–7 neuronal cells (Ishii *et al*. 2009) and down-regulated by a GnRH receptor agonist in the αT_3-1 gonadotroph cell line (Bae *et al*. 2014). However, recent data have also revealed that pituitary *Mt1* expression is unaltered in adult rats treated with a GnRH receptor antagonist and also in $Egr1^{-/-}$ mice (Bae *et al*. 2014). It is therefore clear that further work is required to fully elucidate the mechanisms controlling melatonin sensitivity in developing gonadotroph cells.

Synchronisation of foetal circadian rhythms by maternal melatonin

Circadian clocks have been widely reported in foetal and neonatal individuals of model species (reviewed in Seron-Ferre *et al*. (2012)). Moreover, these clocks are synchronised (entrained) by maternal factors, during the early stages of development before the SCN receive neuronal innervation from the retina (Stanfield & Cowan 1976, Mason *et al*. 1977).

Much of the evidence for maternal melatonin in perinatal circadian entrainment has derived from studies of the Syrian hamster, which possesses more melatonin receptors in the SCN of foetal and neonate animals than adults (Duncan & Davis 1993, Gauer *et al*. 1998). Whereas behavioural rhythms of adult hamsters appear insensitive to melatonin (Hastings *et al*. 1992), neonate hamsters are readily entrained to melatonin injections (Grosse *et al*. 1996). Remarkably, injection of pregnant mothers entrains rhythms of foetal pups, demonstrating the effect of melatonin and its ability to cross the placenta (Davis & Mannion 1988). Evidence for the role of SCN melatonin receptors in this process comes from elegant

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transplantation studies. Lesioning of the SCN in adult hamsters renders them arrhythmic, but transplantation of foetal SCN tissue restores behavioural rhythms that can be entrained by melatonin (Grosse & Davis 1998).

Pharmacological uses of melatonin

Chronobiotic effects

The ability of exogenously administered melatonin to phase shift human circadian rhythms was described in the 1980s (Arendt *et al*. 1985). If given (0.5–10 mg p.o.) before the natural rise of endogenous melatonin, phase advances in sleep, core body temperature, melatonin and prolactin have been observed (Deacon & Arendt 1995, Krauchi *et al*. 1997, Rajaratnam *et al*. 2003). By contrast, melatonin administered in the early biological morning (i.e. 1–4 h after the core body temperature nadir) can produce phase delays in circadian timing. This ability of melatonin to advance or delay clock timing depending on the biological time of administration has been described in terms of a phase response curve (PRC) (Lewy *et al*. 1992, Middleton *et al*. 1997, Revell & Eastman 2005, Burgess *et al*. 2008). The magnitude of the phase shift is dose-dependent (Deacon & Arendt 1995, Burgess *et al*. 2010).

The phase shifting effects of melatonin have been utilised in the treatment of circadian rhythm sleep–wake disorders in which the sleep/wake cycle is desynchronised from the circadian timing system, reviewed in Arendt & Skene (2005). Appropriately timed melatonin has been shown to alleviate symptoms of jet lag and night shift work. Melatonin is also the treatment of choice for non-24-h sleep–wake disorder suffered by totally blind people with no conscious light perception (Skene & Arendt 2007). In this condition, melatonin entrains the free-running non-24-h circadian rhythms including the sleep–wake cycle leading to increased night sleep duration and a reduction in the number and duration of daytime naps. Melatonin (0.3–5 mg p.o) has also been used in the treatment of delayed sleep–wake phase disorder (DPSD), with dosing in the early biological evening (5–6.5 h before DLMO) proving most effective (Nagtegaal *et al*. 1998, Mundey *et al*. 2005), presumably since this maximises melatonin's phase advancing effect according to the published melatonin PRCs.

A great deal of effort has focused on trying to optimise melatonin's phase shifting effect by investigating the best time of administration (biological time and clock time), the lowest effective dose, the optimal treatment regimen (duration), frequency of dosing (set or staggered) and type of formulation (fast or slow release) (reviewed in Arendt *et al*. (2008)). More research is still needed so that these parameters are optimised for each circadian rhythm sleep–wake disorder.

Acute pharmacological effects

Exogenous melatonin causes an immediate drop in core body temperature, reduced alertness and increased tiredness (Deacon *et al*. 1994). Studies suggest that these acute effects are more pronounced if melatonin is given during the day when endogenous melatonin production is low/undetectable (Dollins *et al*. 1994). Transient sleepiness produced following melatonin ingestion before bedtime most likely accounts for the reduced sleep latency reported in several studies (Zhdanova *et al*. 1996, Lemoine *et al*. 2007). The effect of melatonin on polysomnographic sleep is less consistent with studies showing conflicting results (reviewed in Turek & Gillette (2004)).

Melatonin agonists

The similarity in pharmacology between the MT1 and MT2 receptors has hampered the identification of selective agonists to MT1 or MT2. Current melatonin agonists being developed have high affinity at both the MT1 and MT2 receptors, e.g. agomelatine (S20098, Servier), ramelteon (TAK-375, Takeda), LY156735 (Eli Lilly), tasimelteon (VEC-162, Bristol-Myers Squibb Co, licensed to Vanda). For reviews of these melatonin agonists the reader is referred to (Turek & Gillette 2004, Zawilska *et al*. 2009). These melatonin agonists are in various stages of development and drug registration. Unfortunately it is unclear how the efficacy of these novel agonists compare directly with melatonin in clinical trials since head to head comparison with melatonin is not a prerequisite for drug registration.

Perspective/future areas of research

This review has primarily dealt with the generation and function of physiological rhythms of pineal melatonin synthesis, which results in the rhythms of melatonin in the blood. Whereas the timing of the endogenous melatonin rhythm has been a major focus of the published literature, what determines the amplitude of the melatonin rhythm is less well studied. Melatonin amplitude, whilst consistent within an individual, is highly variable between individuals, declines with age and is acutely suppressed by light at night, as previously described.

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Our recent research has shown reduced melatonin amplitude in type 2 diabetes mellitus compared with age and weight matched controls (Mantele *et al*. 2012), consistent with epidemiological data inversely associating melatonin concentration with insulin signalling (McMullan *et al*. 2013) and a broader literature linking melatonin signalling with glucose homeostasis (Peschke 2008, Karamitri *et al*. 2013). In this and other scenarios, understanding the physiological relevance of melatonin rhythm amplitude therefore warrants further investigation and may provide novel insights into the physiological roles of melatonin.

One powerful novel tool to understand the mechanisms underlying links between melatonin, circadian rhythms, sleep and metabolism is metabolic profiling, or metabolomics. We are currently using liquid chromatography mass spectrometry to characterise 24-h metabolite rhythms and the effect of sleep and sleep deprivation on the human metabolome (Ang *et al*. 2012, Davies *et al*. 2014). This will help to better understand melatonin, circadian timing, sleep−wake regulation and associated physiological pathways.

Declaration of interest

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

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