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Circadian regulation of reproduction: from gamete to offspring

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Abstract

Few challenges are more critical to the survival of a species than reproduction. To ensure reproductive success, myriad aspects of physiology and behaviour need to be tightly orchestrated within the animal, as well as timed appropriately with the external environment. This is accomplished through an endogenous circadian timing system generated at the cellular level through a series of interlocked transcription/translation feedback loops, leading to the overt expression of circadian rhythms. These expression patterns are found throughout the body, and are intimately interwoven with both the timing and function of the reproductive process. In this review we highlight the many aspects of reproductive physiology in which circadian rhythms are known to play a role, including regulation of the estrus cycle, the LH surge and ovulation, the production and maturation of sperm and the timing of insemination and fertilisation. We will also describe roles for circadian rhythms in support of the preimplantation embryo in the oviduct, implantation/placentation, as well as the control of parturition and early post natal life. There are several key differences in physiology between humans and the model systems used for the study of circadian disruption, and these challenges to interpretation will be discussed as part of this review.

Key words:

Reproduction, circadian rhythm, clock genes, fertility, ovary, parturition.

1. CIRCADIAN REGULATION OF REPRODUCTION: *from gamete to offspring*

1.1. Introduction

The challenge posed by the environmental oscillation of day and night has driven the evolution of organisms across diverse phyla with an endogenous timekeeping mechanism that measures daily time. This 'clock' permits the anticipation of daily environmental changes, allowing the appropriate modifications of behaviour and physiology. These oscillations are referred to as circadian, coming from the Latin *circa* for 'around' and *dies* for 'day'. In mammals, the most obvious circadian rhythm is the rest/active cycle, with changes in sleep and activity occurring at predictable times of day. However, circadian rhythms pervade all aspects of mammalian physiology, with everything from the cellular redox state through to endocrine and autonomic circuits oscillating predictably across 24 hours. A more formal definition of circadian rhythms could be "the external expression of an internal timing mechanism that measures daily time" (Reppert and Weaver, 2001).

For the survival of a species, nothing is more important to an organism than successful reproduction. Consequently, any advantage that is able to improve the chances of reproductive success is conserved. For animals living in temperate zones, an ability to detect and respond to changing day length is crucial, thereby ensuring reproduction occurs at an appropriate time of year. The complex processes required to decode the seasonal changes in day length, and either suppress or drive fertility, have been reviewed previously (see (Ikegami and Yoshimura, 2012). In this review however, we will discuss how time of day and the circadian system play a role in non-seasonal reproduction. We will review the literature investigating a role for the circadian clock in the broad spectrum of reproductive processes, from oestrus cycles, ovulation, movement of the embryo down the reproductive tract, implantation/placentation, fetal growth and parturition. This leads to the obvious question to be addressed in this review; does circadian disruption lead to poor reproductive outcomes?

1.2. The mammalian circadian timing system

Rather than being a direct response to the external environment, circadian rhythms are generated through self-sustaining endogenous clocks than can maintain time in the absence of external cues. At the centre of this system is the suprachiasmatic nucleus (SCN). This bilateral structure, located in the anterior hypothalamus, immediately dorsal to the optic chiasm, is responsible for the establishment of endogenous rhythms (Ralph et al., 1990). Appropriate synchrony to the external light/dark cycle is achieved through both direct and indirect neural connections linking the retina to the SCN (Miller et al., 1996). Lesions of the SCN eliminate behavioural rhythms (Stephan and Zucker, 1972), aspects of which can be restored by the transplantation of fetal SCN tissue into the third ventricle (Sawaki et al., 1984).

Generation of circadian rhythms within the SCN occurs at the level of individual cells (Herzog et al., 1998; Welsh et al., 1995). At the heart of the circadian pacemaker resides a transcriptional feedback loop, whereby the rhythmic transcription, translation and feedback of a series of 'core clock' genes occurs over 24 hours (Shearman et al., 2000). The process begins when the transcription factors CLOCK and BMAL1 heterodimerise, enter the nucleus and by binding to an E-box (CACGTG) in the promoters, drive the transcription of the *period* (*Per1*, *Per2*, *Per3*) and *cryptochrome* genes (*Cry1*, *Cry2*) (Gekakis et al., 1998; Travnickova-Bendova et al., 2002; Yoo et al., 2005). Upon translation, these proteins form a complex with casein kinase 1δ/ε, then enter the nucleus and inhibit their own transcription (Kume et al.,

1999). The phosphorylation of PER by casein kinase 1δ/ε alters the stability of the complex, delays accumulation, and thus regulates the timing of suppression (Keesler et al., 2000). The CLOCK/BMAL1 heterodimer also differentially drives expression of the orphan nuclear receptors, REV-ERBα/β and RORα/β/γ, whose proteins in turn compete to bind with ROR response elements (RRE) on the *Bmal1* promoter, either suppressing or inducing transcription respectively (Guillaumond et al., 2005; Preitner et al., 2002; Sato et al., 2004; Takeda et al., 2012). Together, these interlocked transcriptional feedback loops, which take 24 hours to complete, provide the foundation for the establishment of molecular circadian rhythms (Figure 1).

The timing of molecular rhythms within individual cells of the SCN is synchronised through interneuronal peptidergic signals, which ensure a coherent and robust phase (Maywood et al., 2006). However, oscillations of clock gene expression within SCN neurons must be translated into a form that conveys rhythmicity to the whole organism. Early ablation and transplant studies demonstrated the importance of both humoral and neural connections in the transfer of rhythmic information to the rest of the body (Silver et al., 1996). Behavioural rhythms such as locomotor activity are controlled in part by secreted factors from the SCN such as arginine vasopressin (AVP) and prokineticin 2 (PK2), whereas many endocrine and autonomic rhythms are dependent upon neural connections. The SCN has afferent connections with various hypothalamic regions including interneurons of the medial hypothalamus, neuroendocrine neurons in the paraventricular nucleus (PVN) and arcuate nucleus (ARC), and pre-autonomic neurons in the PVN (Kalsbeek et al., 2011). Through this series of connections, the SCN can regulate arousal and sleep regulatory centres, as well as control endocrine and autonomic targets (Kalsbeek et al., 2006).

Through these mechanisms, the rest of the body receives temporal information. However, rather than being slaves to the SCN, peripheral tissues also express circadian rhythms of gene expression and function. Importantly, individual cells within the majority of peripheral tissues have been shown to rhythmically express the full range of core clock genes in a self-sustained manner (Balsalobre et al., 1998; Yamazaki et al., 2000). Furthermore, through CLOCK/BMAL1 driven expression of transcription factors and functional proteins that contain the appropriate E-box in their promoter, up to 10% of the transcriptome (Akhtar et al., 2002; Panda et al., 2002), and up to 20% of the proteome (Reddy et al., 2006) is rhythmic. The suite of rhythmic output genes differs between tissues, allowing circadian control of function and activity appropriate for each tissue. Additionally, this tissue specific rhythmicity can regulate the responsiveness of these peripheral targets to various stimuli, including incoming temporal information from the SCN (Oster et al., 2006; Ungar and Halberg, 1962).

1.3. Circadian rhythms and the control of the follicular/luteal cycle

For the successful initiation of pregnancy a series of events need to be tightly coordinated; in the ovary the primordial follicles need to develop and mature, the triggering of ovulation needs to take place and appropriate mating behaviour needs to coincide with the release of the mature oocyte to allow for fertilisation to occur. In the late follicular phase, plasma estradiol concentrations increase, as does the pulsitile frequency of LH release. As the dominant follicle reaches the mature pre-ovulatory stage, the influence of estradiol on GnRH secretion changes from inhibitory to stimulatory, resulting in a concerted release of GnRH from the medial peri-optic area (POMA), a subsequent sustained increase in LH release from the anterior pituitary leading to the release of the oocyte from the ovary. There is convincing evidence that the SCN is intimately involved in these events.

The SCN receives external light information via a direct neural pathway from the retina to the ventrolateral 'core' of the SCN (Moore and Lenn, 1972), which in turn communicates with the dorsomedial 'shell' utilising the neurotransmitters vasoactive intestinal peptide (VIP) (Maywood et al., 2006), gamma-aminobutyric acid (GABA), arginine vasopressin (AVP) and gastrin releasing peptide (GRP) (Maywood et al., 2011; Moore et al., 2002; Tanaka et al., 1997). In its role of gating ovulation to a particular time of day, the ventrolateral SCN projects to the GnRH containing neurones of the POMA utilising VIP (de la Iglesia et al., 1995; van der Beek et al., 1997a; van der Beek et al., 1993; van der Beek et al., 1997b). The dorsomedial SCN, which contain receptors for sampling plasma estrogen concentration (Vida et al., 2008), communicates with the rostral periventricular preoptic area (RP3V), which is comprised of the periventricular preoptic nucleus (PeN) and the anteroventral periventricular nuclei (AVPV), utilising AVP (Vida et al., 2010; Watson et al., 1995; Williams et al., 2011). This region then projects to the POMA utilising kisspeptin as a neurotransmitter, to stimulate GnRH release. The dorsomedial SCN also communicates with the ARC, which projects to the POMA, also utilising kisspeptin. However, in rodents the ARC only expresses inhibitory ERβ receptors and is inhibited by high plasma estradiol levels. As such, this pathway is not considered to play a role in the induction of the LH surge mechanism, although it may have a role in maintaining the pulsatile secretion of LH (Oakley et al., 2009). The SCN also projects to the gonadotropin inhibitory hormone (GnIH, also known as RFRP3) positive cells of the dorsomedial nucleus, which then project to the POMA to inhibit GnRH release ((Kriegsfeld et al., 2010) for review of this pathway).

The increase in estradiol levels as the follicles develop leads to a selective increase in synaptogenesis between SCN projections and GnRH positive cells and the induction of kisspeptin expression in the RP3V (Vida et al., 2010), likely through the ERα receptor (Smith et al., 2005) and further upregulated by the clock controlled transcription factor DBP (Xu et al., 2011). The elevation in estradiol also upregulates gap junction formation in the SCN (Shinohara et al., 2000), increases the sensitivity of the SCN to light stimulation (Abizaid et al., 2004) and sustains activity within the SCN (Tsukahara, 2006), particularly in the dorsomedial region through the ERα receptor and downregulation of the inhibitory ERβ receptor (Vida et al., 2008). This increase in activity is the likely cause of the observed advance in behavioural rhythms on the evening of proestrus (Wollnik and Turek, 1988). It is possible the transcription of GnRH is also under the regulation of the clock genes via TTF1 (Matagne et al., 2012), however the observed *in vivo* oscillation is very small. Together these inputs change the effect of estradiol into inductive to GnRH release, increasing the GnRH concentration in the portal veins and leading to the subsequent release of LH and ovulation.

Humans and other primates share many of the neural structures and functions described above for rodents, although there are key differences, particularly with respect to the source of kisspeptin signalling to the POMA (reviewed in (Plant, 2012)). While kisspeptin is present in the AVPV of the monkey (Rometo et al., 2007; Smith et al., 2010) and human (Hrabovszky et al., 2010; Rometo et al., 2007) and expression is increased by elevated plasma estradiol (Smith et al., 2010), surgical isolation of this region in the rhesus monkey does not abolish the estradiol induced LH surge (Knobil, 1974; Krey et al., 1975). In contrast, the infundubular nucleus (the primate equivalent of the rodent ARC) expresses kisspeptin, is inducible by estradiol (Smith et al., 2010), and lesions prevent the estradiol induction of LH release (Plant et al., 1978).

The importance of the SCN in ovulation has been widely studied in mammals following the reports that SCN lesions abolish ovarian cyclicity in rats (Gray et al., 1978; Mosko and

Moore, 1979). Grafting of fetal SCN, which restores wheel running rhythmicity, fails to restore ovarian rhythms suggesting that circadian regulation of LH release is dependent upon intact neuronal signalling (Silver et al., 1996). In rats, disruption of signalling between the ventrolateral and dorsomedial SCN by administration of barbiturates on the afternoon of proestrus prior to the transition from inhibition to stimulation of GnRH release, delays it for 24 hours (Everett and Sawyer, 1950). Some primates appear to be less sensitive to this perturbation (Knobil, 1974), although it is not clear if this also applies to humans.

Uncovering the role for VIP in this process is challenging, since it is involved in both communication within the SCN (Maywood et al., 2007) and signalling from the SCN to other brain nuclei, including the GnRH containing neurones of the POMA (Smith et al., 2000; van der Beek et al., 1997a). Infusion of VIP into the third ventricle transiently delayed the LH surge and ovulation (Weick and Stobie, 1992; Weick and Stobie, 1995). VIP applied in the early evening phase delayed the SCN both *in vivo* and *in vitro* (Albers et al., 1991; Piggins et al., 1995; Reed et al., 2002; Reed et al., 2001) suggesting that it delays the transduction of a positive signal to the GnRH positive cells from the SCN via the SCN-AVPV pathway. There is evidence from brain slice experiments that VIP increases the neuronal firing rate in GnRH containing neurones (Christian and Moenter, 2008), indicative of GnRH release. However, expression of the VIP receptor was not determined on the recorded cells, and VIP may have been acting indirectly, removing inhibition from another synaptic pathway. It is surprising in the context of the above studies that for *in vivo* models, anti-VIP antibody administration or infusion of VIP antisense oligonucleotides both prevent ovulation and impair the LH surge (Harney et al., 1996; Van-Der Beek et al., 1999). Possible mechanisms include (a) prevention of direct signal transduction from the SCN to the POMA (van der Beek et al., 1997a; van der Beek et al., 1997b), (b) reduction of the synchronicity of the SCN, impairing signalling to the RP3V (Maywood et al., 2006) or (c) prevention of the inhibitory signal from the ventrolateral SCN reaching the GnIH cells within the dorsomedial nucleus (Kriegsfeld et al., 2010). The role of AVP is also important, particularly for signal transduction from the ventrolateral SCN, and the SCN control of ovulation could be bypassed by timed administration of AVP in both SCN lesioned and SCN intact animals (Palm et al., 1999; Palm et al., 2001). The genetic loss of AVP results in perturbed estrus cycles and lower litter sizes, although this could be confounded by more general systemic metabolic dysfunction in these rats (Boer et al., 1981).

Mice lacking a functional *Bmal1* gene show irregular estrus cycles (Ratajczak et al., 2009) and impaired ovulation (Boden et al., 2010). The ovaries of these animals are responsive to exogenous gonadotropins, although with a lack of central rhythm, it is surprising these animals are able to generate a LH surge. Even mice with less profound circadian disruption such as the *Clock*$^{\Delta 19}$ and *Clock*$^{\Delta 19}$*+MEL* mice, which are able to maintain central rhythms while peripheral tissues are arrhythmic (Kennaway et al., 2007), display irregular estrus cycles (Kennaway et al., 2005; Miller et al., 2004) which are exacerbated by continuous darkness (Dolatshad et al., 2006). The *Per1* or *Per2* null mutants are initially able to reproduce normally but develop irregular estrus cycles as they age (Pilorz and Steinlechner, 2008), and *VPAC* null mice, similar to *Clock*$^{\Delta 19}$ mutant mice, have irregular cycles exacerbated by continuous darkness (Dolatshad et al., 2006). Rats and mice, kept in constant light develop disrupted estrus cycles (Campbell et al., 1976), albeit with less penetrance than the above listed mutant and null mouse models, and require significantly longer exposure to become affected. Bright light exposure is known to reduce the size of the LH surge (Bronson and Vom Saal, 1979) and decrease the number of oocytes ovulated, although only in melatonin replete strains of mice (Bronson, 1979; Goto et al., 1989), suggesting a sensitising role for this hormone. The disruption of circadian rhythms in humans through exposure to

shiftwork has been associated with irregularity of menstrual cycles (Knutsson, 2003; Labyak et al., 2002; Lawson et al., 2011; Su et al., 2008), with an increased extent or duration of exposure leading to greater incidence of cycle disruption.

1.4. Circadian rhythms and control of the ovary

In the previous section we discussed the circadian rhythm of LH release and its importance in ovulation. The sensitivity of the ovary to LH also changes across 24 hours, with maximal responsiveness consolidated to middle of the night of proestrus in rats (Sellix et al., 2010). The post pubertal cycling ovary maintains a rhythm in gene expression (Gras et al., 2012) , and while there are discrepancies in the literature, there is consensus that the granulosa and thecal cells of the follicle (early, preantral and antral), glandular tissue and in some studies the corporal luteal cells express the core clock genes rhythmically (Fahrenkrug et al., 2006; Karman and Tischkau, 2006), whereas for other cell types (oocyte, stromal fibroblast) the evidence is less clear. Some of this complexity may be explained by steroid (Rubel et al., 2012) and LH/FSH (Shimizu et al., 2012) influences on the expression of the core clock genes, as well as other accessory clock genes (e.g. DEC1/2 by LH/FSH) (Yamada et al., 2004). The DEC proteins repress the gene expression and transcription factor activity of BMAL1 (Hamaguchi et al., 2004; Honma et al., 2002) potentially resulting in the gain or loss of rhythmic gene expression transiently across the female reproductive cycle.

1.5. Circadian rhythms and the generation of sperm

The generation of sperm is highly regulated, but whether rhythmicity is critical for testes function has not been resolved. At the whole organ level, clock gene expression is apparent but either constitutive (Alvarez et al., 2003) or rhythmic but with clock genes such as *Per* and *Bmal1* in phase rather than in antiphase as with other tissues (Bebas et al., 2009). It was suggested that the clock genes may have an alternate, non-rhythm generating role in rapid growth or tissue remodelling (Alvarez et al., 2003; Morse et al., 2003). In seasonally reproducing hamsters, long day length initiates testicular recrudescence and induction of *Per1* mRNA, while short daylength drives gonadal regression and induced *Bmal1* mRNA expression (Tong et al., 2004). Clock genes may have a role at specific stages in sperm development. For example, in mice, expression of *Per1* mRNA was limited to stage 7-10 spermatids, whereas *Clock* mRNA was expressed in the spermatogonia and spermatocytes up until the first meiotic division (Alvarez et al., 2003; Bittman et al., 2003; Morse et al., 2003). Other core (*Bmal1*, *Rev-erbα*, *Per3*) and accessory (*NPAS2*, *DBP*) clock genes were expressed in the testes, and there was some evidence they may be rhythmically expressed, but these rhythms were questionable in the testes or not explored in detail (Yamamoto et al., 2004; Zylka et al., 1998). Leydig cells are the source of testosterone production, and it is interesting that animals null for *Bmal1*, *Per2* alone and *Per1/Per2* double mutant mice have low *steroidogenic acute regulatory protein* (*StAR)* gene expression and reduced serum testosterone levels (Alvarez et al., 2008; Kennaway et al., 2012). Plasma testosterone concentration is known to be rhythmic across 24 hours, although in mice this rhythm is absent in some strains (e.g. C57Bl/6) (Lucas and Eleftheriou, 1980). As such, it is unknown if the loss of *Bmal1* or *Per1/2* also abolishes the rhythm in testosterone production.

The corpus and caudal epididymis rhythmically express core clock genes and several effector genes. It was speculated that these genes may have a role in the maintenance of optimal conditions in the lumen for sperm maturation and stability (Bebas et al., 2009). Rhythms in gene expression were also evident in the vas deferens, seminal vesicles and prostate (Bebas et al., 2009), although the importance of these rhythms remains unknown. In humans, there is

no evidence of diurnal variation in sperm parameters (Biljan et al., 2005), which is understandable considering the process of spermatogenesis is considerably longer than 24 hours. There is evidence that sperm quality is impaired in some circadian mouse models (Alvarez et al., 2008; Kennaway et al., 2012), however the effect of shift work on sperm quality has not been well investigated to our knowledge.

1.6. Circadian rhythms and mating behaviour/fertilisation

Humans exhibit rhythmic copulation behaviour, with increased incidence in the late night (Palmer et al., 1982; Refinetti, 2005) and a minor peak in the early morning (Palmer et al., 1982). For women, the fertile window begins between 3-6 days prior to the LH surge (Wilcox et al., 1995), and its length depends on the longevity/viability of sperm deposited. Passage of the sperm into the uterus is facilitated by an increase in the hydration and permeability of mucus of the reproductive tract, in response to increased estradiol 2-3 days prior to the LH surge (Katz et al., 1997). The LH surge in humans occurs between midnight and 8am (Cahill et al., 1998; Kerdelhue et al., 2002; Khattab et al., 2005). Following the LH surge, both estradiol and LH decrease rapidly, leading to a more challenging environment to sperm motility and consequent impaired fertilisation capacity (Wilcox et al., 1995). Ovulation occurs 12-48 hours after the LH surge (Luciano et al., 1990; Vermesh, 1987) with fertilisation possible shortly thereafter. The importance of coincident ovum release and coitus is not well established, but in mice, where the timing of mating and ovulation are closely matched, the longer mating occurs after ovulation, the poorer the reproductive outcome (Sakai and Endo, 1988). In humans, a similar delay would coincide with the changes in mucus hydration. Even bypassing this barrier though use of Intrauterine Insemination, which eliminates the impact of abnormal mucus or other physical characteristics of the tract, has a 5-10% pregnancy rate (Khattab et al., 2005), compared to 37% from intercourse at an appropriate time (Wilcox et al., 1995), suggesting that delayed fertilisation in humans may be detrimental.

The broad time spans mentioned above are the result of large sampling intervals for the various parameters due to the invasiveness of the monitoring. Furthermore, many of the subjects were attending assisted reproduction clinics due to infertility, so the extent that the results can be used to instruct us about normal human fertility can be questioned.

1.7. Circadian rhythms and the passage of the embryo through the oviduct/uterus

The oviduct has a significant role in the support, protection and signalling of the early embryo, secreting an ensemble of factors into the lumen, including hormones, nutrients, protease enzymes and their regulators. The composition of the oviductal fluid has been studied extensively (Aviles et al., 2010; Gardner and Leese, 1990), although the dynamic changes in secretion at least beyond the early responses to mating are less well characterised. It is known that the oviduct rhythmically expresses both the core clock genes and several transcription factors and enzyme regulators important for the protection of the embryo (Kennaway et al., 2003), although the full extent of the oviductal transcriptome, particularly in the early pregnancy state, has not been extensively evaluated. In almost all other tissues examined, 5-20% of the transcriptome is rhythmically expressed (Kita et al., 2002; Storch et al., 2002), and it is likely that the oviductal transcriptome would follow this trend.

While the oviduct and the luminal environment surrounding the embryo is rhythmic, it is still unclear how important this is for the early embryo, and when rhythmic gene expression of the embryo is initiated. It is known that clock genes are expressed in the embryo up to the 2 cell

stage (Hamatani, 2004), presumably as remnants of maternal transcription, and that their expression decreases to very low levels before increasing again following transcription of the embryonic genome (Amano et al., 2009; Johnson et al., 2002). The core clock genes do not, however, show signs of rhythmic expression even at the mature blastocysts stage. Moreover embryonic stem cells are also non-rhythmic, and rhythmicity only appears as cellular differentiation progresses. In contrast, the reprogramming of neuronal stem cells to become pluripotent stem cells abolishes rhythmic gene expression (Yagita et al., 2010).

1.8. Circadian rhythms and implantation

Implantation depends upon the synchronised development of a competent blastocyst and a uterine environment receptive to attachment. In mice the uterus is receptive to implantation on day 4 post insemination and in humans between days 7 and 10 post insemination. Clock genes and their proteins are rhythmically expressed within the luminal epithelium, stroma and myometrium of the uterus (Akiyama et al., 2010; Horard et al., 2004; Nakamura et al., 2005; Ratajczak et al., 2010), including over the period of uterine receptivity (Uchikawa et al., 2011). Clock gene expression is altered by ovarian steroid hormones (He et al., 2007; Nakamura et al., 2005; Nakamura et al., 2008), with progesterone increasing *Npas2, Clock*, *Cry1* and *Per1* and decreasing *Rev-erbβ* and *RORγ* mRNA expression via progesterone receptor binding (Rubel et al., 2012). Additionally, *Vegf* mRNA (which has an E-box in the promoter) is rhythmically expressed over the peri-implantation period (Uchikawa et al., 2011). It is tempting to speculate that clock genes play a role in implantation in response to signals from ovarian hormones. If this were the case, then disrupting circadian rhythms through mutation or knock out of clock genes would be expected to reduce implantation success. *Bmal1* knockout mice display complete failure of implantation, despite the presence of viable blastocysts in the oviduct after mating to wild type males. This is largely due to insufficient luteal steroidogenesis, however exogenous progesterone can only partially (38%) rescue the implantation failure, and in those animals with implantation sites, there were 35% fewer than the controls and fetal growth restriction was evident (Ratajczak et al., 2009), suggestive of implantation failure. Middle age *Per1* mutant mice also have reduced implantation sites compared to wild types (Pilorz and Steinlechner, 2008).

Initiating circadian disruption through exposure to altered photoperiod has also been demonstrated to influence pregnancy success. Exposing mice to either phase delays or advances of the photoperiod throughout pregnancy, with the first shift occurring between fertilisation and implantation leads to a profound reduction in pregnancy success, although the exact stage of fetal loss is unclear (Summa et al., 2012). Additionally, mice exposed to photoperiods of 26 h (13L:13D, which is outside the level of entrainment) during pregnancy had significantly reduced number of implantation sites (Endo and Watanabe, 1989). Further work is required to determine the mechanisms, if any, through which circadian rhythms and clock genes control apposition, attachment and penetration, processes necessary for successful implantation.

1.8.1. Circadian rhythms and the placenta

There may also be a role for clock genes in the development and functions of the placenta. Frigato *et al* demonstrated that *Per2* mRNA is rhythmically expressed in a human extravillous trophoblast cell line following serum shock (Frigato et al., 2009). These same cells displayed a circadian rhythm in cell proliferation, which was accompanied by a robust oscillation in E-box controlled genes regulating cell-cycle (*wee1*) and cell motility (*stathmin*) (Lunghi et al., 2011). This is preliminary evidence for a role of circadian clocks in the process of trophoblast proliferation and migration, steps critical for successful placentation.

There is mixed evidence for intrinsic oscillations in clock gene expression in the term placenta. Rat placenta on day 22 lacked *Per1* mRNA rhythmicity in the labyrinth, while the maternally derived decidua had a high amplitude *Per1* mRNA rhythm (Akiyama et al., 2010). In contrast, Ratajczak *et al* demonstrated rhythmicity of *Cry1*, *Per1* and the clock controlled gene *DBP* mRNA (but not *Bmal1*, *Cry2* or *Per2*) in whole mouse placenta at day 17, and when explants of placental tissue were placed in culture, robust rhythms of PER2:luciferase bioluminescence activity emerged (Ratajczak et al., 2010). Wharfe and colleagues found that when analysed separately, both the labyrinth and junctional zones of the placenta expressed all of the core clock genes, with *Bmal1*, *Per1* and *Per2* displaying time of day and zone dependent changes (Wharfe et al., 2011). However, the pattern of expression was unusual in that *Bmal1* and *Per1/Per2* were not expressed in antiphase as would be expected in a fully functioning transcriptional feedback loop.

While the evidence for a core clock feedback loop operating in the near-term placenta in altricial species is limited, there is evidence for other components being rhythmically expressed. For example, both the glucocorticoid receptor, and components of the placental glucocorticoid barrier (*11β-hsd1* and *Abcb1b*) are rhythmically expressed in the rat placenta (Waddell et al., 2012), as is the expression of the melatonin receptor, *MT1* (Lee et al., 2003). We speculate that these rhythms are driven not by local clock mechanisms within the placenta, but rather in response to rhythmic maternal secretion of these hormones.

There have been limited assessments made as to the impact of circadian disruption, either through environmental manipulations or through mutant/knockout models on the placenta. Gozeri however found that exposure to either constant light or darkness, or 6L:6D photoperiod throughout pregnancy reduced both placental and fetal rat weight, and increased placental edema, fibrin accumulation and leukocyte infiltration (Gozeri et al., 2008).

1.9. Circadian clocks during fetal development

The prenatal environment is inherently circadian. The developing fetus is exposed to fluctuating levels of temperature, substrates and hormones that oscillate over the 24 hour day, driven largely by the maternal system through her endogenous behaviour, feeding, and endocrine rhythms. The fetus, however, expresses its own rhythms including heart rate, respiratory movements and hormone secretion. To understand the role of this rhythmicity in fetal development, and the implications of disruption to these oscillations, we will first discuss the development of the fetal circadian system. For a more detailed analysis of this topic see the excellent reviews of Seron-Ferre and colleagues (Seron-Ferre et al., 2012; Seron-Ferre et al., 2001; Seron-Ferre et al., 2007).

In the rat, the SCN is formed from embryonic day 14 (ED14) through to ED17, with synaptogenesis developing through the late prenatal and early postnatal period (Moore, 1991). Rhythms of glucose utilisation, *vasopressin* mRNA and neuronal firing rate are all detectable in the fetal rat SCN in the days leading up to birth (Reppert and Schwartz, 1984b; Reppert and Uhl, 1987; Shibata and Moore, 1987). Clock gene mRNA is detectable in the SCN as early as ED19 (Sladek et al., 2004), yet rhythmicity of expression may not appear until after birth (Kovacikova et al., 2006; Sladek et al., 2004) (however see also (Ohta et al., 2002)). The circadian system develops rapidly over the postnatal period as incoming terminals from the retina to the SCN begin to form around Post Natal Day 1 (PND1) (Speh and Moore, 1993), with light responsiveness also occurring at this time (Ferguson and

Kennaway, 2000a; Ferguson and Kennaway, 2000b; Ferguson et al., 2000; Leard et al., 1994; Weaver and Reppert, 1995). However, SCN afferent connections responsible for the control of overt circadian rhythms develop later, with the rhythmic secretion of hormones such as melatonin not occurring until the second week of life (Tamarkin et al., 1980).

In humans, non-human primates and sheep, development of the suprachiasmatic nucleus advances further during the prenatal period. In humans the SCN is formed by week 18 of gestation (Reppert et al., 1988). In non-human primates, rhythms of glucose utilisation as well as *Bmal1* and *Per2* mRNA expression become detectable in the SCN at 90% gestation (Reppert and Schwartz, 1984a; Torres-Farfan et al., 2006), whereas in fetal sheep, rhythms of c-FOS protein in the SCN appear as early 25% gestation (Breen et al., 1996). Overt circadian rhythms including fetal heart rate, fetal movements and plasma cortisol are readily detectable in human fetuses (de Vries et al., 1987; Mirmiran et al., 1992; Seron-Ferre et al., 2001), as is plasma melatonin, cortisol and prolactin in fetal sheep (McMillen et al., 1987; Zemdegs et al., 1988), although melatonin rhythms may be due to maternal sources rather than rhythmic fetal pineal secretion (McMillen and Nowak, 1989). The fact that SCN driven rhythms of body temperature and oxygen consumption are rhythmic in preterm infants born at 80% gestation, despite exposure to a steady state environment, suggests the human fetal SCN is functioning well before birth (Bauer et al., 2009; Mirmiran et al., 1990). However, rhythmic secretion of melatonin in human babies does not appear until 9-12 weeks of age (Kennaway et al., 1992), probably because the neural connections linking the SCN to the pineal develop gradually after birth.

Peripheral clocks also develop slowly through the late prenatal and early postnatal period. Microarray studies on fetal liver collected from mice between ED18 and ED19 in animals kept in constant darkness reveal little evidence of rhythmic clock gene expression (Li et al., 2012), consistent with previous reports in a variety of peripheral tissues (Dolatshad et al., 2010; Sladek et al., 2007). There has, however, been an intriguing report of daily oscillations in the fluorescence of *Per1* driven luciferase in mice *in vivo* at ED19, although the actual organ expressing this rhythmicity is unclear (Saxena and Willital, 2008). Similarly, rhythmic *Per1* luciferase activity in fetal liver *ex vivo* can be observed at ED22 in rats (Ohta et al., 2008). More importantly, when access to food was restricted to only 4 hours during the day in the mother, advancing her behavioural and liver rhythmicity (but not SCN rhythmicity), fetal *Per1* luciferase activity was similarly advanced by 4.7 hours in the SCN and 7.4 hours in the liver, suggesting maternal feeding and activity schedules can entrain fetal clocks.

Rhythmic clock gene expression has been observed within the fetal adrenal during late gestation. In the capuchin monkey at 90% gestation, the fetal adrenal expresses *Bmal1* and *Per2* mRNA rhythmically and in anti-phase, which is accompanied by rhythmic production of dehydroepiandrosterone sulphate. Interestingly, melatonin receptor *MT1* mRNA is also rhythmically expressed in these animals (Torres-Farfan et al., 2006). Similarly, in the rat, antiphase rhythms of adrenal *Per2* and *Bmal1* mRNA expression is evident at ED18, as is rhythmic *StAR* and *MT1* mRNA and fetal plasma corticosterone (Torres-Farfan et al., 2011). These rhythms persist in culture, and when melatonin is applied during the late subjective night, there is a phase delay in *Per2*, *Bmal1* and *StAR* mRNA expression. These results demonstrate not only that the fetal adrenal possesses intrinsic oscillator capacity, but it is responsive to melatonin. Melatonin, being lipophilic, freely crosses the placenta unaltered (Schenker et al., 1998), and together with feeding signals and body temperature, likely acts to confer time of day information to both the SCN and peripheral tissues in the fetus.

If the fetus is driven by the maternal circadian system, what then is the effect of maternal circadian disruption? As mentioned previously, exposure of pregnant mice to frequent phase advances in the photoperiod throughout gestation dramatically reduces the number of litters born (Summa et al., 2012). In our laboratory, we exposed pregnant rats to reversals of the photoperiod every 3-4 days throughout gestation and for the first week after birth (Varcoe et al., 2011). Surprisingly, this treatment had no effect on litter size, birth weight or growth of the offspring to weaning. However, when these animals were assessed for a range of metabolic parameters as adults, age and gender dependent increases in adiposity, hyperleptinaemia and alterations to glucose metabolism, were observed. These results suggest that maternal circadian disruption can program perturbed metabolic homeostasis in the offspring. Similarly, the importance of rhythmic maternal melatonin secretion during pregnancy and lactation in the development of metabolic pathways in the offspring was highlighted by the observation of poor glucose tolerance in offspring born to pinealectomised rats (Ferreira et al., 2012). Furthermore, supplementation of the dams' nocturnal drinking water with melatonin prevented these perturbations.

These results highlight the importance of considering the maternal circadian environment during pregnancy. Given the increasing incidence of shift work in our society, large numbers of pregnant women are exposed to conditions disrupting not only patterns of sleep and activity, but also a range of endogenous circadian rhythms including melatonin secretion, body temperature, and the timing of food consumption. These disruptions may have implications for the developing fetus. It is however inherently difficult to address these concerns through epidemiological studies. Large variations in the types of shifts, durations of rest between shift changes, stage of gestation for when shift work commences/ceases etc make it extremely difficult to dissect the relationship between shift work during pregnancy and long term health outcomes. There is, however, some evidence that maternal shift work can increase the risk of poor pregnancy outcomes including small for gestational age babies, miscarriage and preterm birth (Abeysena et al., 2009; Lawson et al., 2009; McDonald et al., 1988; Whelan et al., 2007; Zhu et al., 2004a; Zhu et al., 2004b), although a recent meta-analysis suggests the relative risk associated with shift work is small (Bonzini et al., 2011). Again, a major limitation of many studies is that the amount, type, and timing of shift work exposure were often not considered.

1.10. Circadian rhythms and the timing of birth

In humans, parturition often involves various degrees of medical intervention, obscuring the natural course of events and hence the timing of both labour initiation and delivery. Nevertheless, it is clear that the timing of birth is more common around late night/early morning, in both term and pre-term human births (Cagnacci et al., 1998; Cooperstock et al., 1987; Glattre and Bjerkedal, 1983; Lindow et al., 2000). Circadian rhythms of birth frequency can also be observed in a wide range of animal species from non-human primates to rodents, with the timing of birth appropriate for the evolutionary niche of each species. Rats most commonly give birth during the day (Plaut et al., 1970), and importantly, the timing of parturition can be manipulated in this species through the modification of the photoperiod (Lincoln and Porter, 1976), demonstrating the role of a light-sensitive clock mechanism in this process. Similarly, ablation of the SCN in rats disrupts the timing of parturition (Reppert et al., 1987). When mice lacking *Bmal1* expression in the myometrium were analysed for the timing of parturition, only 64% gave birth exclusively during the night of PND19, whereas 92% of control mice gave birth during this window (Ratajczak et al.,

2012). These results demonstrate the importance of rhythmic clock gene expression, specifically within the uterus, for the regulation of timing of birth.

Recent reviews have highlighted the role of melatonin in driving circadian rhythmicity of parturition (Olcese, 2012; Olcese et al., 2012). Obviously melatonin cannot be the only signal that drives these rhythms, as the majority of laboratory mice do not synthesise melatonin (due to mutation in 2 key enzymes (Ebihara et al., 1986)), yet still give birth during the early hours of the morning (Roizen et al., 2007). Nevertheless, when female rats are pinealectomised, and hence don't produce melatonin, the timing of birth is deregulated, and occurs independent of time of day (Takayama et al., 2003). Importantly, melatonin administration during the time of normal endogenous nocturnal secretion can restore the circadian rhythm of birth. Despite some conflicting results as to the exact location and receptor subtype, melatonin receptors have been described in the rat endometrial stroma (Zhao et al., 2000) and myometrial smooth muscle cells (Steffens et al., 2003). Similarly, both melatonin binding sites, and melatonin receptors have been isolated in the myometrium of both pregnant and non-pregnant women (Schlabritz-Loutsevitch et al., 2003). In rats, melatonin can be considered tocolytic, as administration inhibits local prostaglandin synthesis, and slows uterine contractility *in vivo* and in the presence of oxytocin *in vitro* (Abd-Allah et al., 2003; Gimeno et al., 1980; Hertz-Eshel and Rahamimoff, 1965). This is consistent with the timing of birth occurring during the day when melatonin secretion is absent. Seemingly in contradiction to this, humans are statistically more likely to give birth during the night, a time when melatonin secretion is high. It has been argued however, that in humans melatonin is uterotonic, increasing myometrial contractions by augmenting the actions of oxytocin and increasing myometrial gap junctions (Olcese et al., 2012). Intriguingly, melatonin receptors are up-regulated in the myometrium of women who had entered labour compared to those who had not (Sharkey et al., 2009).

This raises the question of whether melatonin suppression can reduce uterine contractions. Olcese and colleagues have provided preliminary evidence that this is the case, with nocturnal bright light exposure, and the suppression of melatonin this creates, leading to a reduction in uterine contractions of pregnant women >38 weeks gestation (Olcese et al., 2012). Further work is required, but this raises the intriguing possibility that the bright light of the delivery ward may in fact reduce the strength of uterine contractions and delay labour, or alternatively, whether suppression of melatonin could be used as a tool to delay labour in preterm situations.

1.11. Summary and conclusion

In this review we have highlighted how the circadian timing system is interwoven with reproductive physiology, either as a subtle modulator, an important regulator, or as an indispensable component of the process. The importance of successful reproduction for the survival of a species has led to a robust system able to adjust to and overcome arising challenges. As such it is of great interest that the disruption of a single clock gene (particularly *Bmal1*) is able to significantly perturb reproductive function. Furthermore, there are critical windows of opportunity (pre- and peri-implantation) where circadian disruption impairs reproductive success. While animal models have been invaluable for increasing our understanding of the interactions between neural, hormonal and behavioural systems involved in reproduction, there still is a need for better human studies. Given mounting evidence that circadian rhythm disruption affects the health of the mother, father and the developing child, particularly in terms of their reproductive development and metabolic health this is a field in need of further investigation.

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1.13. Conflicts of interest:

The authors have no conflicts of interest to declare.

1.14. References

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