Clocks underneath: the role of peripheral clocks in the timing of female reproductive physiology

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The central circadian pacemaker in the suprachiasmatic nucleus (SCN) is a critical component of the neuroendocrine circuit controlling gonadotropin secretion from the pituitary gland. The SCN conveys photic information to hypothalamic targets including the gonadotropin releasing hormone neurons. Many of these target cells are also cell autonomous clocks. It has been suggested that, rather than being singularly driven by the SCN, the timing of gonadotropin secretion depends on the activity of multiple hypothalamic oscillators. While this view provides a novel twist to an old story, it does little to diminish the central role of rhythmic hypothalamic output in this system. It is now clear that the pituitary, ovary, uterus, and oviduct have functional molecular clocks. Evidence supports the notion that the clocks in these tissues contribute to the timing of events in reproductive physiology. The aim of this review is to highlight the current evidence for molecular clock function in the peripheral components of the female hypothalamo-pituitary-gonadal axis as it relates to the timing of gonadotropin secretion, ovulation, and parturition.

Keywords: clock gene, reproduction, fertility, circadian rhythm, ovary, uterus, oviduct, pituitary gland

INTRODUCTION

Generating a complete picture of the timing systems role in pregnancy and parturition requires examining the molecular clocks role in the timing of events that precede fertilization. The temporal control of ovulation and the events that follow depend in large part on the timing of luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion from the pituitary gland (1). Serum gonadotropin levels display robust diurnal variation (2–4). In nocturnal rodents, LH secretion increases in the afternoon and peaks 3–4 h into the night (3, 5). These rhythms are dependent upon the activity of pacemaker neurons in the suprachiasmatic nucleus (SCN) (6, 7). As with behavior, gonadotropin secretory rhythms persist in constant conditions (8, 9). Neuropeptidergic SCN efferents pass temporal cues from the retina to gonadotropin releasing hormone (GnRH) neurons in the preoptic area of the basal forebrain (10, 11). GnRH stimulates gonadotropin secretion from the pituitary gland via the portal vasculature. The timing of the ovulation-inducing surge of LH depends on this neuroendocrine network (12, 13). It has long been the view that this complex circuit is the sole source for timing cues in the female reproductive system (5, 14).

The biochemical substrate for circadian oscillations is a transcriptional-based autoregulatory negative feedback loop of interacting clock gene transcription factors, including at its core the transcriptional enhancer bmal1 and the repressors period (1, 2) and cryptochrome (1, 2) (15). In addition to SCN neurons, the pituitary, ovary, uterus, and oviduct are each comprised of cell-autonomous circadian clocks [see Figure 1; (16–25)]. However, a functional role for the clock in these tissues, particularly with regard to the timing of ovulation, implantation, and parturition, has yet to be thoroughly defined (24, 25). The clock in the ovary may play a significant role in the timing of ovulation, steroid hormone synthesis, follicular growth, and differentiation (26–30). Clock genes in the uterus and oviduct have been implicated in the processes of implantation, embryo maturation, development of the fetus, and eventual parturition (18, 23, 31–33). Others have linked circadian clock function to reproductive physiology, with particular emphasis on steroid hormone biosynthesis (34–36). Mutations altering clock gene expression have a substantial impact on reproductive function in both rodents (31, 33, 37, 38) and humans (39).

Taken together, these data indicate that while oscillators in the basal hypothalamus play a critical role, the peripheral components of the hypothalamo-pituitary-gonadal (HPG) axis may also contribute to the timing of reproductive physiology. Disruption of the molecular clock in these peripheral tissues or reduced synchrony amongst these oscillators may be a factor in diseases that cause infertility (40). The goals of this review are: (1) highlight the evidence for molecular clock function in the peripheral tissues of the HPG axis and (2) briefly speculate on the physiological ramifications of disrupted molecular clock function as it relates to ovulation and the events that follow. For the purpose of this mini-review, we will avoid discussion of the complex and well-described role of the clock genes in photoperiod-dependent reproductive physiology. Our intention is to shed light on the most salient and current evidence for peripheral clock function in basic female reproductive physiology and highlight potential impacts of circadian disruption on fertility.
FIGURE 1 | Circadian clock function in the peripheral tissues of the female HPG axis. The central circadian clock in the suprachiasmatic nucleus (SCN) drives rhythmic GnRH secretion and subsequent gonadotropin secretion from the pituitary. In addition to these neuroendocrine pacemakers, clocks are also present in the pituitary gonadotroph, uterine endometrium and myometrium, oviduct epithelial cells and ovarian theca, interstitial, and granulosa cells. Clock function has been implicated in GnRH signaling, gonadotropin sensitivity, ovulation, steroid hormone synthesis, embryonic maturation, implantation, and decidualization. Synchronization of central and peripheral oscillators is mediated by several putative humoral and neural cues, driven either directly or indirectly by the SCN. Moreover, feedback signals from the periphery, e.g., steroid hormones of ovarian origin, modulate the timing of the clock in both central and peripheral tissues of the HPG axis.

CIRCADIAN CLOCK FORM AND FUNCTION: THE PITUITARY GONADOTROPH

Both circadian and ultradian patterns of LH secretion have been described in female mammals (41–45). Examination of LH release from isolated pituitary explants and pituitary cell cultures indicated that individual gonadotrophs or a subpopulation of differentially regulated gonadotrophs may be autonomous circadian oscillators (44, 46). More recently several groups have described cell autonomous clock gene expression in the pituitary gland (16, 22, 47–52). Kakar and colleagues provided the earliest evidence for a functional clock gene expression in the pituitary gland (16, 22, 50, 51). Kakar and colleagues provided the earliest evidence for a functional clock gene expression in the pituitary gland with the revelation that GnRH induces per1 expression in gonadotroph cell lines (53). Olcese and colleagues subsequently determined that per1, but not per2, gene expression was activated by GnRH receptor (GnRHR) through MAP kinase-dependent signaling (54). This group also identified seven clock-gene target sequences in the mouse GnRHR promoter and determined that both BMAL1 and CLOCK bind to and activate GnRHR expression (22). Most importantly they were able to co-localize PER1 with LH in pituitary cells in situ (22). Further, using siRNA they confirmed that suppression of bmal1 expression effectively reduced GnRHR mRNA. Finally, this group reported that GnRHR mediated activation of early growth response protein-1 (EGR-1) also leads to activation of per1 expression (51).

In addition to GnRHR signaling and receptor gene expression, the molecular clock may also regulate physical changes in the pituitary. That is, gonadotroph proliferation changes during the estrous cycle (55) and exhibits a diurnal rhythm, with a peak in S-phase near 14:00 h (56). A rhythm of gonadotroph proliferation with a period equal to the 4-day estrous cycle and a peak on estrous was described in rats (57). Together, these data indicate that the circadian clock in gonadotrophs may regulate rhythms of cell proliferation, secretory responses to gonadotropins, and gonadotropin gene expression. Recently, it was reported that only per1 mRNA was rhythmically expressed in human pituitary glands (58). Surprisingly, a rhythm of PER1 protein was not detected. Finally, it was recently reported that, unlike global bmal1 deletion, cell-specific deletion of bmal1 in gonadotrophs had no effect on the amplitude and timing of gonadotropin secretion (52). Mice...
with gonadotroph-specific bmal1 KO had normal fertility, though the duration of the estrous cycle was increased (52). These data suggest that molecular clock function in regions upstream (basal hypothalamus) or downstream (ovary) may be more critical for normal reproductive function in mice.

**Circadian Clock Form and Function: The Ovarian Follicle**

Rhythmic expression of clock genes in the ovary has been observed in rat (19–21, 26), mouse (59), quail (60), and chicken (61). In 2006 a pair of independent studies reported rhythms of clock gene expression in the rat ovary (19, 20). These studies revealed that gonadotrophin exposure *in vivo* induced cyclic expression of bmal1 and per2 mRNA in the ovaries of hypophysectomized prepubertal rats (20). They also observed diurnal rhythms of per1 and per2 expression that persisted across the reproductive cycle (19). Further, these authors confirmed rhythms of clock gene expression within large preantral follicles, small antral follicles, graafian follicles, and corpora lutea. The same group have subsequently confirmed this finding (29). More recently it was reported that rhythms of clock gene expression are only present in mature isolated granulosa and luteal cells (21, 26, 62, 63). Comparable results have also been reported in quail, with only the largest preovulatory follicles showing rhythmic per2 expression (60). The absence of rhythmic clock gene expression in immature or differentiating cells has also been reported in the thymus and testis (34). These data suggest that circadian rhythms of clock gene mRNA are “activated” at some point during differentiation of follicular cells. Studies on the ontogeny of the clock support this notion, though there is also limited evidence that rhythmic gene expression can persist even in the absence of a functional molecular clock (64, 65). New evidence suggests that the appearance of robust rhythms of clock gene expression in mature follicles may be due to FSH-dependent expression of gap junction proteins (30). Disruption of cell-to-cell communication via gap junction blockers (e.g., lindane) reduces the amplitude and lengthens the period of PER2-luc expression in rat granulosa cells (30). These data indicate that gonadotropin-dependent communication among follicular cells may play a role in the appearance and/or maintenance of clock controlled gene (CCG) expression.

Gonadotropins clearly affect the timing and amplitude of clock gene expression in ovarian cells (20, 26, 27, 29, 63). We have systematically characterized the phasic nature of sensitivity to gonadotropins in cultured rat granulosa cells (27). The physiological significance of these results is puzzling, given the transient nature of the follicle (29). Rather than mediating entrainment, it is likely that the impact of gonadotropins on the timing of clock gene expression reflects the indirect influence of receptor-mediated activation of cAMP-dependent signaling pathways (66).

Despite all the evidence for a molecular oscillator in follicular cells, the physiological significance of the ovarian clock is largely a mystery. Our own work reveals that the timing of ovulation may depend on a window of sensitivity to gonadotropins. We have observed a circadian rhythm of sensitivity to exogenous LH-treatment following suppression of endogenous LH secretion with a selective GnRHR antagonist (28). We have more recently determined that this rhythm is not dependent on the mature pattern of ovarian steroid hormone secretion or a fully developed and sexually mature neuroendocrine system, as we have observed the same rhythm in juvenile mice primed with equine gonadotropins (unpublished observation). These data indicate that rhythmic sensitivity of the ovary to gonadotropins may be an innate feature of the mature preovulatory follicle, driven in part by the ovarian clock.

How might the clock in follicular cells regulate the timing of sensitivity and/or prepare the preovulatory follicle for ovulation at the appropriate time? It is well known that the LH surge induces a significant change in gene expression within the granulosa and theca cells of the follicle (66–68). However, evidence for rhythmic expression of LH-responsive genes is limited. Several genes induced by LH signaling in the ovary are possible CCG candidates. LRH-1 (also known as CYP7A promoter binding factor) was first cloned and identified as an orphan nuclear receptor in the liver (69). In the ovary, LRH-1 expression is limited to the granulosa cell layer and is implicated in the regulation of steroid hormone biosynthesis and bile acid production (70). Recently, LRH-1 was shown to bind directly to CLOCK (71) and act synergistically to drive CLOCK:BMAL1 mediated transcription in the liver (71). In the ovary, LRH-1 has been implicated in the control of steroid biosynthesis in granulosa cells through direct activation of cytochrome P450 side chain cleavage (CYP11A1) transcription (72). Thus, LRH-1 may represent a mechanistic link between LH receptor signaling and the molecular clock in follicular cells.

In response to the LH surge enzymatic pathways responsible for follicular rupture are activated (67, 73, 74). A significant step in the response to LH is an increase in the level of prostanooids, including prostaglandin E2 (PGE2) and PGF2α (74). The rate-limiting enzyme for prostaglandin (PG) synthesis is cyclooxygenase-2 [COX2; (74)]. COX2 catalyzes the conversion of arachidonic acid to PGs and evidence suggests that COX2 expression is regulated by E-box promoter elements (74). In addition, treatment with PGE2 *in vivo* has been shown to phase shift the rhythm of per1, *d-element binding protein (dbp)*, and *rev-erba* mRNA expression in the heart, liver, and kidney (75). Most recently, it was revealed that luteinized or “mature” granulosa cells do in fact have robust circadian rhythms of *ptgs2* and *lhcr* gene expression that are disrupted and in some cases abolished by *bmal1* siRNA (76). Together, these data suggest that an increase in COX2 and LH receptor expression and/or PG activity preceding the arrival of the LH surge may allow for predictive changes in ovarian cells in anticipation of ovulation.

It is also clear, from work in both rodents (30, 31, 36, 76) and birds (35), that the circadian clock plays a considerable role in the amplitude and timing of steroid hormone biosynthesis. Circadian rhythms of steroidogenic acute regulatory protein (StAR), 3βeta-hydroxysteroid dehydrogenase (3β-HSD), 11α-hydroxylase, and aromatase (cyp19) have been observed in mature granulosa cells (30, 76). These rhythms are altered or abolished following treatment with *bmal1* siRNA (76). Further, *bmal1−/−* mice have abnormally low levels of progesterone secretion due to reduced STAR expression (31).

**The Circadian Clock in the Uterus and Oviduct**

Evidence for circadian clock function in the uterus is limited but supports a contribution of the uterine clock in the process of
implantation, development of the conceptus, and eventual parturition (17, 23, 31, 33). Johnson and colleagues were the first to describe rhythmic clock gene expression in the uterus (17). Subsequent investigations determined that uterine cells were in fact semi-autonomous clocks (21, 32, 77). The timing of clock gene expression in the uterus appears to be affected by the reproductive cycle (78) and stimulation with ovarian steroids (79, 80). Global knockout of the core clock gene bmal1 disrupts implantation, alters the level of steroid hormone synthesis, and compromises fertility (31). Further, targeted deletion of bmal1 gene expression in the myometrium abrogates normal implantation (33). Finally, it was recently reported that circadian clock gene expression in per2 of several clock genes and CCGs including bmal1 alters the level of steroid hormone synthesis, and compromises the uterus and pituitary gland. Extension of this approach to the ovary and oviduct will provide a more complete picture of clock function in these tissues.

As with the uterus, initial evidence for a functional clock in the oviduct was provided nearly a decade ago by Johnson and colleagues (17). In the 10 years following few studies have advanced our understanding of clock function in this tissue. In fact, only one additional study by Kennaway and co-workers has examined clock function in the oviduct. These authors described rhythms of several clock genes and CCGs including per2, bmal1, dbp, plasminogen activator inhibitor-1 (PAI-1), and rev-erb in the oviduct, supporting the notion that the embryo is exposed to rhythmic environmental conditions during passage to the uterus (18). Further the authors suggest that rhythmic secretory activity of epithelial cells may be critical for embryonic development. As with the ovary, additional functional studies of clock dependent physiology are needed to confirm the role of the clock in both the uterus and oviduct.

SUMMARY

The aim of this brief review is to discuss our current understanding of molecular clock function in the peripheral tissues of the mammalian female reproductive tract. It should be clear that, while we know a great deal about the location and character of the clock, our understanding of peripheral clock function is rather limited. The discovery of nearly ubiquitous clock gene expression in the tissues of the HPG axis suggests widespread and diverse physiological function. The female reproductive tract is fertile land for these explorations as it is elegantly organized, thoroughly integrated by positive and negative feedback, and temporally robust in its output. Using targeted deletion approaches (e.g., Cre-Lox system), investigators have begun to more thoroughly and intensively characterize molecular clock function in the uterus and pituitary gland.

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