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REVIEW

Biological rhythms and fertility: the hypothalamus–pituitary–ovary axis

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Abstract: In addition to normal physiological processes, a number of pathological conditions exhibit diurnal and seasonal fluctuations in their incidence. These biological rhythms are generated by the circadian clocks that adjust their functions and adapt to the habitat. Misalignment of biological rhythms and disrupted functions of the circadian clocks may eventually have a negative impact on reproduction, which is the focus of this review. A large body of literature from animal studies has demonstrated the role of core clock genes and clock-controlled genes in regulation of reproductive events. In contrast, only a few studies, mostly epidemiological ones, suggest that perturbations of the circadian clock functions, eg, due to shift work or jet lag, compromise human reproduction.

Keywords: animal, circadian, diurnal, human, reproduction

Introduction

The lives of many species, including humans, have been ancestrally regulated by biological rhythms. Indeed, fertility and reproduction in animals follow specific circadian and seasonal rhythms, which are aimed to guarantee that mating opportunities and birth of offspring occur during the most favorable season in terms of climate and food availability, as to assure the best offspring survival. This process is finely regulated by a complex and elegant interaction between perception and elaboration of environmental stimuli and activation of endogenous functions according to a rhythmic pattern. All this is made possible through the accurate synchronization imposed by an endogenous internal clock. The central pacemaker of circadian and seasonal rhythms in mammals is the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus. It has an endogenous rhythm with a near-24-hour period,[1] termed a circadian rhythm, which is receptive and adaptive to time-giving cues from the habitat.

The seasonal and circadian rhythms of fertility and reproduction are apparently less obvious in humans, especially in modern societies and cultures where work and social situations impose their own rhythms on life, and where the availability of contraception and other birth control options allow controlling and planning timing of reproduction. Maintaining this biological regulation has become more and more complicated, as a consequence of the numerous social stimuli superimposed upon the original biological rhythms. Even in such a context, when the entrainment between environmental and social cues and endogenous physiological functions has become more and more challenging, biological rhythms continue to run and regulate reproduction and many other functions of our body. Misalignment and disruption of biological rhythms

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may eventually negatively impact on several physiological functions, including reproduction. Therefore, it is intuitive how the consequences of the disruption of biological rhythms need to be understood and properly addressed.[2]

The aims of this article are to review the current knowledge on the biological rhythms of reproduction and fertility and to discuss about the possible effects of their disruption.

Biological rhythms: definition and examples

Many physiological functions follow the rhythm of ~24 hours, ie, a circadian rhythm. In addition, there are biological rhythms that have a shorter (ie, ultradian) or longer (ie, infradian) period than that of 24 hours. By definition, circadian rhythms persist in constant environmental conditions, such as light–dark and temperature transitions, demonstrating that they are generated by endogenous oscillators rather than in response to external cues. However, the endogenous oscillators need properties that enable them not only to anticipate the seasonal changes in ambient temperature and the photoperiod but also to adapt to sudden changes in these conditions as well as to reset due to socially imposed changeovers of the timetables.[3]

Examples of physiological circadian rhythms include not only the sleep–wake cycle and the core body temperature cycle but also the production and secretion of hormones such as cortisol and melatonin. In addition, it appears that many reproductive events follow a circadian rhythm,[4] so that spontaneous live births occur more frequently in the morning and that the onset of labor during the night leads to a shorter duration of labor in the analysis of >1,800 deliveries for which only singleton pregnancies having a spontaneous onset of contractions and the intended vaginal delivery were included.[5]

There is also circannual fluctuation in many physiological rhythms that are evidenced as a seasonal pattern. It appears that the photoperiod may influence the number of arginine vasopressin (AVP)-releasing neurons in the SCN, the number is higher in the autumn than in the summer.[6,7] Other neurotransmitters (eg, serotonin) seem to follow a seasonal pattern in their hypothalamic levels, and the circadian rhythm of melatonin secretion varies in relation to the photoperiod, ie, follows a seasonal pattern.[4] These fluctuations contribute to a number of pathological conditions such as sleep and mood disorders that exhibit a seasonal variation in their incidence and symptom worsening.[8] Directly as such or mediated by changes in body weight or pathological conditions, the seasonal fluctuations might still have an effect on human reproduction.[8,9] However, it is not known whether dysfunctions of the circadian clocks or certain clock gene variants or their de novo mutations have any causal role in these conditions.[10]

Molecular mechanisms of biological rhythms

Stimuli from the habitat, such as the wavelengths of light exposure and their intensity, are perceived by the retina, conveyed via the retinohypothalamic tract to the SCN, and processed as a function of time. The SCN sends humoral and neuronal signals to a range of target effectors located in the brain as well as in peripheral sites, such as the pineal gland, pituitary, thyroid, heart, liver, uterus, and ovaries.[11,12] Several different neurotransmitters participate in the communication from the SCN cells, such as AVP and the vasoactive intestinal peptide (VIP). It is of note here that vasopressin-releasing neurons in the SCN follow themselves a circadian and seasonal rhythmicity in their synthesizing activity.[6,7]

The core or the so-called canonical molecular mechanisms underlying the circadian rhythmicity are autonomously generated by a specific set of the so-called clock genes and their protein products.[13] They form interlocking transcription–translation feedback loops within a cell with the whole cycle lasting ~24 hours.

The SCN is the principal, master, or central circadian clock within the organism.[14] Clock genes and their protein products in each tissue play a role in driving, heretofore unknown for some tissues, clock-regulated genes. The nature of these genetic targets is largely unknown to date, and for some it is not known how they act to regulate rhythms in the tissue. The way the circadian rhythmicity is synchronized from the level of tissues to the level of the organism is not completely clear, but the SCN and its neurons located in the "shell" actively participate in this process throughout the organism.[14] These actions use, eg, the connections of the SCN to other brain areas to regulate the core body temperature, and they involve, via the sympathetic regulation, the control of synthesis and subsequent excretion of melatonin from the pineal gland into the circulation. However, it seems that the SCN organization is more complex than a simple "core" and "shell" arrangement.[11]

In addition to the SCN, a rhythmic expression of clock genes has been uncovered also in a range of peripheral tissues, such as the liver, kidney, heart, lung, spleen, skeletal muscles,[15] as well as the uterus,[16] ovaries,[17,18] and oviduct,[19] indicating protein coding but not necessarily telling about functional relevance. Furthermore, in the brain and peripheral

tissues such as reproductive tissues, many genes other than the aforementioned core clock genes are rhythmically expressed, because either they have in their promoter E-box sequences for binding rhythmically expressed CLOCK/BMAL1 complexes or they are rhythmically regulated by other specific clock-controlled transcription factors.[20,21] Taken together, these observations reinforce the idea that peripheral mammalian cells are autonomous oscillators that actively contribute to the generation and maintenance of biological rhythms. However, a tight synchronization is needed between the central and peripheral oscillators, and this process is believed to be mostly, but not exclusively, driven by the SCN.[22]

Biological rhythms and fertility: the hypothalamus–pituitary–ovary axis

As mentioned earlier in the "Introduction", fertility and reproduction processes are characterized by seasonal and circadian rhythms in many species. Seasonal rhythmicity is commonly driven by the photoperiod (ie, the length of the day), which acts as the main time giver to regulate the endogenous circadian production of melatonin, in turn regulating fertility and reproduction. As an example, puberty onset is inhibited by short day length in rats with the practical meaning of favoring fertility and reproduction during the season of the year when food availability is at its maximum. Furthermore, in rats, the estrous cycle follows a clear circadian rhythmicity, so that the luteinizing hormone (LH) surge starts in the afternoon of proestrous, and ovulation and mating occur 6 hours after darkness. In other words, the timing of the LH surge, and therefore the timing of ovulation, is highly determined.[23,24] As for other seasonal and circadian rhythms, the timing of reproductive function in mammals, including humans, is also orchestrated mainly by the SCN as part of the hypothalamus–pituitary–ovary (HPO) axis. The functioning of the HPO axis is a good example of the tight interconnections and circadian synchronization between neural, endocrine, and neuroendocrine signals that result in the ovarian cycle, ie, the main component of reproduction in female mammals.

The ovarian cycle is regulated by gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, which in turn regulates the secretion of gonadotropins, ie, follicle-stimulating hormone (FSH) and LH from the pituitary. Because the ovarian sensitivity to the LH surge, required for the ovulation to occur, is limited to a narrow time window, the timing of the GnRH secretion must be finely coordinated. A combination of positive hormonal, ie, the circulating levels of gonadal steroids, feedback signals from the dominant ovarian follicle and circadian timing signals from the SCN controls this regulation, eventually leading to the release of GnRH levels required for the onset of the LH surge. In humans, GnRH neurons extend from the preoptic area through to the infundibular nucleus (homolog to the arcuate nucleus in other mammalian species) of the hypothalamus, and the communication from the SCN to the GnRH neurons is mediated by neurotransmitters such as AVP and VIP.[25] GnRH secretion is time dependent, and kisspeptin (KISS) has an effect on the ultradian rhythm of GnRH gene transcription and protein secretion.[26]

Interestingly, *Avp* expression in the SCN is regulated by CLOCK and BMAL1, and it rhythmically oscillates during the day in both wild-type and *Clock* mutant mice.[27] However, wild-type mice have higher SCN *Avp* expression than mutant mice. Similarly, the expression of the AVP 1a receptor in the hypothalamus is reduced in *Clock* mutant mice. Furthermore, in *Clock* mutant, but not in wild-type mice, treatment with AVP injections in the preoptic area on the afternoon of proestrous produce a significant increase in LH levels (ie, an LH surge), possibly mediated by the AVP 1a receptor.[27] These findings suggest that AVP participates in the circadian timing signals of the LH surge in mice. Specifically, Miller et al suggest that in mice AVP is released from the SCN neurons projecting to hypothalamic GnRH neurons with a daily circadian pattern.[27]

More precisely, VIP-mediated projections from the ventrolateral SCN reach the GnRH neurons in the medial preoptic area. Additionally, AVP-mediated projections from the dorsomedial SCN communicate to the anteroventral periventricular (AVPV) nucleus, which in turn induces GnRH release via KISS-mediated projections to medial preoptic area.[28] However, only in the presence of high levels of estradiol, as during the proestrus, a possible hyper-regulation of AVP 1a receptors in the hypothalamus generates a status of enhanced sensitivity to AVP, eventually resulting in the LH surge. In this model, the low SCN expression of *Avp* in *Clock* mutant mice produces no timing signal to the GnRH neurons, which in turn are less responsive to AVP because of their low expression of AVP 1a receptors.[27] The GnRH cells also act as endogenous autonomous oscillators that probably regulate the time of sensitivity to SCN communication. The rhythmic expression of circadian clock genes (*Bmal1*, *Clock*, *Cry1*, *Cry2*, *Per1*, *Per2*, *Per3*) and their protein products in GnRH-secreting neurons is well established,[29–34] as it is the alteration of the GnRH rhythmic secretion caused by the disruption of clock genes, eg, decreased mean pulse frequency in *Clock-Δ19* mutants.[29]

Other mechanisms possibly involved in the generation and transmission of timing signals for the ovulation include environmental signals of dark and light, respectively, conveyed from the retina to the SCN and transmitted to the pineal gland, leading to melatonin secretion or inhibition. In humans, the photoperiod and thus light exposure via the eyes have endocrine effects and to some extent take part in regulation of reproductive cycles as well.[35,36] Melatonin is known to influence reproduction by binding melatonin receptors that are rhythmically expressed in GnRH-secreting cells and downregulating hypothalamic GnRH gene expression,[30,37] and by interacting with receptors expressed in the ovaries.[38] It is of note that melatonin is also produced in peripheral sites, including reproductive organs such as the ovaries (eg, in the granulosa cells and oocytes) and the placenta, and as such actively influencing the development of the fetal SCN.[39]

Steroids from the adrenal are also likely to contribute to the regulation of the expression of pituitary and ovary clock genes. Similarly, ovarian steroids regulate the expression of clock gene in the ovaries, as well as in the uterus and pituitary.[40] In fact, clock genes are widely expressed across the HPO axis, ie, the pituitary, ovaries, oviduct, and uterus, and the clock proteins are likely to play an active role in the timing of reproductive functions, such as follicular development, ovulation, steroid hormone synthesis, implantation, and development of the fetus.[41] All these mechanisms participate in the regulation of the timing of reproduction through stimuli from the external light–dark transitions and those from the autonomous central and peripheral circadian clocks.

Biological rhythms of fertility across the HPO axis: the role of VIP and KISS

As mentioned earlier, the SCN communicates with the GnRH neurons through a combination of monosynaptic (VIP neurons) and multisynaptic (AVP–KISS) pathways, which is possibly involved in the initiation of the LH surge as follows.

VIP-secreting neurons from the SCN project to the hypothalamic GnRH-secreting neurons. VIP null mutant mice have been shown to have reduced fecundity, ie, fewer pups, less time being pregnant or nursing, and abnormal reproductive function, ie, irregular and longer estrous cycles being characterized by a longer duration of diestrus/metestrus but shorter proestrus not always followed by the estrous phase and a reduced number of oocytes released after proestrus.[42] Additionally, VIP null mice had a normal period and a normal amplitude of *Per2* rhythm in uterus and ovaries, but the amplitude was blunted in the SCN and pituitary. Furthermore, the phase of *Per2* rhythm was normal in the SCN and ovaries but advanced in the uterus and pituitary. These results suggest that VIP alterations primarily affect the SCN rather than the ovaries. However, VIP null mice had similar estradiol and maximum LH concentrations in proestrus as wild-type mice, and it is not known whether these mice have a persistent LH rhythm.[42] These findings, along with the observation of maintained through reduced fecundity in VIP null mice, suggest that alternative mechanisms are implicated in the circadian initiation of the reproductive cycle. This hypothesis is further supported by the fact that the GnRH-releasing neurons do not express the estrogen receptor needed for the estrogen positive feedback to be effective, and by the fact that the neurons reached by VIP projections from the SCN constitute only a small proportion of GnRH-secreting neurons.

Recent findings strongly point to the involvement of the AVPV and its related KISS-mediated communication in the circadian regulation of the reproductive cycle. To date, a number of studies have shown the essential role of KISS in puberty onset and the maintenance of fertility. Lesions of AVPV cells in rats cause the disruption of KISS-mediated communication and eliminate the estrous cycle.[43] Furthermore, KISS knockout mice or mice lacking KISS cognate receptor GPR54 do not have LH surge or GnRH neuron activation.[44,45]

The SCN communicates via AVP projections with the AVPV neurons, which in turn project to GnRH-producing neurons by means of KISS. AVPV neurons express estrogen receptor α, thus allowing a fine integration between the circadian SCN regulation and the estrogen-mediated positive feedback from the developing follicle. The secretion of AVP by the SCN neurons follows a circadian rhythm in rodent models: it starts to increase during the first half of the light period and it peaks in the middle of the day, during the sensitive time window before the LH surge. After the peak, AVP secretion declines and reaches a trough in connection with the dark period.[46] Administration of AVP to SCN intact, ovariectomized rats during the second half of the light period does not affect the time of the LH surge but stimulates its amplitude; on the contrary, when administered during the first half of the light period it has no effect on the LH surge.[46] More recently, in their study of ovariectomized hamsters, Williams et al observed that the neuronal activity of KISS cells follows a daily pattern, which is coordinated with the LH surge and is enhanced by the administration of estradiol.[34] In detail, it appears that the ability of KISS to activate GnRH neurons is limited to a specific time window

(in the afternoon), meaning that the GnRH neuron sensitivity to KISS varies during the day and is maximal at the time when the LH surge can be induced. Interestingly, these changes in the sensitivity to KISS are the estradiol-dependent part of estrogen positive feedback system.

In summary, the circadian information from the SCN is partly transmitted to GnRH neurons through AVP-responsive KISS cells located in the AVPV. The time window for the regulation of the LH surge to occur at a certain time of the day is generated through daily changes in the sensitivity of GnRH neurons to KISS, in turn regulated by estradiol.[34] In detail, the circadian rhythm of expression of the KISS receptor GPR54 requires adequate estradiol stimulation, ie, elevated estradiol produced by the dominant follicle for an adequate amount of time, as shown in in vitro hypothalamic GnRH-secreting cells.[33] In the same study, KISS stimulation after estradiol exposure induced significant increases in GnRH secretion, with peaks in correspondence of the aforementioned peak expression of GPR54, while the disruption of endogenous circadian clock activity led to the inability of estradiol to regulate GPR54 expression levels. In other words, it appears that high, ie, suprathreshold, levels of estradiol are necessary to induce the LH surge via the stimulation of GnRH release in a temporal synchronization mediated by SCN signals to the KISS-releasing neurons in the AVPV.

In addition to the AVPV, estrogen-sensitive KISS neurons are also present in the arcuate nucleus, which appears to be equally important for maintaining regular LH surge and estrous cycles.[47] In rats with KISS knockdown within the AVPV, there was a delayed puberty onset, a reduced estrous cyclicity with prolonged estrous cycles (longer estrous and shorter diestrus phases), and a reduced occurrence of the LH surge which was, however, of regular amplitude when it occurred. On the contrary, KISS knockdown within the arcuate nucleus did not affect puberty onset but altered the estrous cycle in a similar way as within the AVPV and caused a decrease in the LH surge amplitude.[47]

In conclusion, as suggested by Williams et al,[34] it is likely that a combination of stimulatory and inhibitory signals project from the SCN to the GnRH neurons in the hypothalamus via an intermediate network. These signals include AVP-mediated projections from the SCN to KISS neurons in the AVPV (stimulatory on the GnRH neurons), projections to the gonadotropin inhibitory neurons in the dorsomedial hypothalamus, as well as possible projections to the GABAergic and glutamatergic neurons in the AVPV. This combination of stimulatory and inhibitory signals, together with direct VIP-mediated efferent projections from the SCN, reaches GnRH neurons, which respond according to the concurrent estradiol milieu.

Biological rhythms of fertility across the HPO axis: animal studies of clock gene expression

Animal studies have been conducted in the recent years to uncover the molecular mechanisms underlying the biological rhythms of fertility in the HPO axis. The most consistent finding of these studies is the rhythmic expression of core clock genes and clock-controlled genes across the HPO axis, ie, the pituitary, ovary, oviduct, and uterus, in addition to the hypothalamic expression described earlier.

Recent studies have shown that gonadotropin-releasing cells in the pituitary are also circadian oscillators with autonomous expression of clock genes.[41] The GnRH released from the hypothalamus in response to circadian SCN signals induces *Per1* expression in gonadotropin-releasing cells; this process occurs through BMAL1- and CLOCK-mediated activation of the GnRH receptor.[48] It is of note that gonadotropic cell proliferation in the pituitary follows a diurnal rhythm and is synchronized with the estrous cycle in normal adult rats.[49] Recently, using a human autopsy dataset, Wunderer et al examined the postmortem pituitaries of 52 individuals deceased for different causes at various times of the day (dusk, night, dawn, or day).[50] Clock gene expression (*Per1*, *Cry1*, *Clock*, and *Bmal1*) was found in the pituitary tissue; however, while the expression of mRNA of *Cry*, *Clock*, and *Bmal1* did not vary in relation to the time of the death, *Per1* mRNA expression was significantly higher in case of death occurring during the day than at dusk, irrespective of postmortem interval, age, or sex. Similarly, the expression of protein products PER1, CRY1, and CLOCK did not differ across the time-of-death groups. The expression of PER1 and CRY1 displayed a different subcellular distribution in relation to the time of the day: although PER1 and CRY1 expression in the cytoplasm was stable across the four time groups, the nuclear expression of PER1 was present during day and at dusk, but not during night or at dawn. CLOCK expression seems not to vary with the time of the day and to be predominantly nuclear rather than cytoplasmic. The authors hypothesized these patterns of expression to be regulated by melatonin.

Animal studies have consistently revealed that clock gene mRNAs such as *Bmal1*, *Per1*, and *Per2* are rhythmically expressed in the ovaries, specifically in mature follicular cells, and their expression is probably regulated by gonadotropin-mediated signals.[40] The internal ovarian clock

significantly contributes to the rhythmic window of ovarian sensitivity to LH and FSH, which in turn regulates the timing of ovulation.[41] In other words, to be effective, the LH surge is synchronized with a specific time window of ovarian sensitivity that is under the influence of estradiol.[51] This synchronization is believed to be the result of a combination between SCN regulation via neural and humoral transmission and the endogenous ovarian regulation via autonomous oscillators.[40] Evidence for a circadian rhythmicity of clock genes in the ovaries was provided by Karman and Tischkau,[18] who examined the expression of *Bmal1*, *Clock*, *Per1*, *Per2*, and *Cry1* in the rat ovaries via 4-hour samples collected through a 24-hour cycle. In the granulosa cells, ie, in growing and antral ovarian follicles, *Bmal1* mRNA expression was 4-hour delayed relatively to *Bmal1* expression in the SCN, with a peak at light onset (ie, at the end of the night) and a trough at light offset (ie, after 12 hours). On the other hand, the expression of *Per2* was in antiphase with *Bmal1* (peaking at light offset) and 4–6 hours delayed relatively to the expression in the SCN. However, the authors failed to find any rhythmic expression of *Bmal1* and *Per2* in the corpora lutea of the rat ovaries.

More recently, He et al examined rat granulosa cells of immature ovaries and found a constant expression of *Per1* through the day; on the contrary, in luteal cells of pubertal female rats, *Per1* expression was cyclic with a peak at light offset.[52] The same study provided evidence for a gonadotropin-mediated regulation of clock gene expression in the ovaries, as FSH acutely induced *Per1* expression in granulosa cells in vitro with a peak within 1 hour. A similar induction was found after the administration of LH in mature granulosa cells, and both FSH and LH seemed to be able to synchronize the circadian rhythm in granulosa cells. Furthermore, Karman and Tischkau demonstrated that, while *Per2* expression did not vary across the estrous cycle, the expression of BMAL1 gene product was higher on the day of proestrus at ZT18 (ie, 8–10 hours after the LH surge) than on the day 1 of diestrus.[18] In total absence of exposure to the LH surge, *Bmal1* and *Per2* mRNA were not rhythmically expressed in juvenile rats, but their rhythmic expression was restored after the administration of exogenous chorionic gonadotropin.

Taken together, these and other findings concerning rat ovaries after denervation are suggestive of the fact that both FSH and LH synchronize the ovarian clock.[53] Among several plausible mechanisms, such as the influence of steroid or LH/FSH signals on core or accessory clock genes,[54] one hypothesis is that the ovarian clock itself (ie, the rhythmic expression of clock genes in the ovaries) modulates the expression of LH/FSH receptors or the timing of hormone secretion.[41] In fact, in addition to the core clock genes, in granulosa cells, the expression of clock-controlled genes (eg, LH receptor, cyclooxygenase-2, and liver receptor homolog 1) oscillates with a circadian rhythmicity regulated by the BMAL1/CLOCK complex and induced by the LH surge.[40,55] For example, *Bmal1* knockdown in rat granulosa cells causes, in addition to the downregulation of core clock gene expression (*Per1*, *Per2*, *Rev-erbα*), the disruption of the circadian expression of several ovarian genes, including the LH receptor gene *Lhcgr*.[56] Similarly, it is plausible, but to date not fully proven, that a circadian clock system also controls the rhythmic expression of clock genes in the theca cells in the ovary.[40]

Similarly to the ovaries, a rhythmic expression of circadian clock genes, possibly maintained through ovarian signals,[28] is evident in the uterus. The role of uterine clock genes is likely essential for reproductive functions such as implantation, fetal development, and delivery.[57] Specifically, in light/dark conditions, the expression of *Per2*, *Cry1*, and *Bmal1* in the uterus of wild-type mice follows a circadian rhythm, with an antiphase profile between *Bmal1* (peak at ZT4, ie, 4 hours after lights-on time) and *Cry1*/*Per2*.[17] Similarly, *Per1* expression in the uterus follows a circadian rhythm, with a 3-hour delay relatively to the SCN rhythm, in nonpregnant rats, regardless of light conditions, ie, the light–dark transitions or constant darkness.[58] The expression of core clock genes (*Per1–3*, *Cry1–2*, *Bmal1*, and *Clock*) was also found in uterine tissues of pregnant mice and rats.[58,59] Interestingly, the circadian expression of *Per1* is maintained across the different stages of pregnancy. On the contrary, the circadian expression of *Per1* is only transiently detectable in decidual tissue, in light/dark conditions only.[58]

The first evidence for the expression of clock genes in the oviduct was also provided by Johnson et al,[59] and further supported by Kennaway et al,[19] who investigated the rhythmic expression of clock and clock-controlled genes in the rat oviduct via 4-hour samples collected over a 24-hour period. In addition to the rhythmic expression of clock genes, they found significant rhythmicity in the expression of clock-controlled genes, such as D site of albumin promoter (albumin D-box) binding protein, Rev-erbα, and plasminogen activator inhibitor-1, suggesting that the embryo is exposed to a circadian rhythmicity, which may be crucial in the early stages of implantation and development. However, no circadian pattern has been detected in trophoblastic cells, supporting previous evidence of limited circadian oscillations in the embryo and fetus. In fact, clock genes are expressed in

the embryo soon after fertilization, but their levels fall at the two-cell stage and increase again probably after the transcription of the embryonic genome with the exception of Clock transcripts, which remain low up to the stage of blastocyst. Finally, clock gene expression in the embryo appears not to be rhythmic.[28,59]

Disruption of biological rhythms across the HPO axis: animal studies

Several pioneer studies have shown that SCN ablation or lesions in rats result in irregular estrous cycles and the inhibition of LH surge and of ovulation.[23,60,61] These results have been confirmed by recent studies of core clock gene mutants and mutant cell lines.

Clock mutant mice seem to have a number of alterations in their reproductive function and fertility.[3,19,62] In detail, *Clock/Clock* mutant mice were found with prolonged irregular estrous cycles, which are characterized by shorter proestrus but longer estrous compared with wild-type or *Clock*$^{/+}$ females.[62] The authors did not find any ovarian anomalies, eg, normal estrogen or progesterone levels on diestrus and proestrus and the development of normal ovarian cells. However, *Clock* mutants had no LH surge on the proestrus day, but only a minor elevation of LH levels, which surprisingly was enough to induce ovulation. This finding supports the idea that the function of the peripheral clock in the ovary, where NPAS2 can substitute for CLOCK, is critical to ovulation. However, in terms of fertility, *Clock* mutant mice had a higher rate of fetal reabsorption and pregnancy failure (eg, failure to enter labor) compared with wild types, probably as a consequence of reduced estrogen and progesterone levels during pregnancy. The authors hypothesized that in *Clock* mutants the daily signal from the SCN to the GnRH neurons is disrupted, possibly through an altered VIP-mediated or AVP-mediated transmission, thus leading to the reproductive anomalies described earlier.[62] These findings were confirmed by a study of *Clock*$^{\Delta 19}$ mice,[17] where the CLOCK$^{\Delta 19}$/BMAL1 dimer is not able to induce transcription, thus leading to impaired rhythmicity in central and peripheral tissues. In *Clock*$^{\Delta 19}$ mice, the rhythmical expression of clock genes in the uterus is lost, and the estrous cycle is prolonged with a prolonged estrous phase, especially in conditions of constant darkness. *Clock* mutant mice also have more delivery problems (eg, a prolonged labor) and more perinatal losses than wild-type mice, especially in constant darkness.[17] Knockdown of *Clock* in the ovaries affects mice fertility, as demonstrated in the decreased number of oocytes spontaneously released on the morning of the estrous stage and in the smaller-than-normal litter size.[63] Of clinical interest, fetal tissues after induced abortion or spontaneous miscarriage at gestational age of 5–9 weeks were analyzed, and it was found that CLOCK protein was reduced in the chorionic villi of spontaneous miscarriage fetuses, as compared with induced abortion fetuses.[63]

A number of studies have consistently shown important reproductive and fertility abnormalities in *Bmal1* null mutant mice, such as late onset of puberty, irregular estrous cycles, absence of proestrus LH surge, implantation failure, delayed embryo development or embryo loss, and loss of rhythmic gene expression in the ovaries.[20,57,64] In detail, Ratajczak et al confirmed previous observations that *Bmal1* null female rats are infertile, as their mating with *Bmal1*$^{+/+}$ males did not result in any litter.[57] Interestingly, *Bmal1* null rats seemed to have an estrous cycle, which however was longer than in wild types; they also had normal ovarian follicular development, ovulation, fertilization, and early embryo development. However, *Bmal1* null rats had lower serum levels of progesterone (but similar levels of estradiol) during the early stages of gestation (ie, at the time of implantation). Even though ovulation occurred in *Bmal1*-defective mice, they had less oocytes and embryos in the reproductive tract compared with intact mice. Because the enzyme catalyzing the rate-limiting step of steroidogenesis, the steroidogenic acute regulatory protein, was almost undetectable in the corpora lutea of *Bmal1* null mice, the authors hypothesized that an impaired steroidogenesis, resulting in low progesterone levels when the uterus is receptive for implantation, rather than altered ovulation, causes the failure of implantation in *Bmal1*-defective mice.

Similar findings were reported by Boden et al,[20] who noticed that heterozygous *Bmal1* mice have normal circadian rhythmicity and fertility, although with high perinatal mortality. On the contrary, *Bmal1* null mice were found to have delayed puberty onset by 4 days, irregular estrous cycles with less time spent in the estrous phase compared with wild-type mice, altered mammary development, smaller ovaries, lower progesterone levels, and fewer ovarian follicles and corpora lutea. Additionally, although they retained their ability to ovulate, they were not able to deliver pups.[20] It is of note that conditional *Bmal1*-knockout female mice, ie, *Bmal1* null mutants only in specific peripheral tissues, eg, in the pituitary,[64] or in the myometrium,[65] are still fertile, although with some reproductive anomalies such as irregular estrous cycle length and abnormal timing of parturition. Chu et al studied conditional knockout mice lacking *Bmal1* in the FSH–LH-secreting cells in the pituitary,[64] and they noticed an elevation in LH levels across all estrous stages and

increased variability in the duration of the estrous cycle but normal reproductive ability. On the contrary, conditional *Bmal1*-knockout female mice lacking *Bmal1* expression in steroidogenic cells of the ovaries, adrenal glands, and pituitary (but normally expressed in liver, muscle, uterus, and oviduct) have normal puberty onset, normal estrous cycle, and ovulation, but the reproductive failure was due to early pregnancy loss as a consequence of implantation failure. As these mutants had lower progesterone levels, the administration of supplemental progesterone was able to rescue implantation. Taken together, these results suggest that the reduced fertility of *Bmal1* null mice is attributable to the steroidogenic components of the ovaries.[66]

On the one hand, studies on *Per1* or *Per2* mutant mice suggested the disruption of circadian rhythms with only minor fertility alterations, such as decreased litter size, increased perinatal mortality, and disruption of the estrus cycle with age.[67,68] In specific, these mutants have normal reproductive function, but fertility rapidly deteriorates with age. In *Per1/Per2* null mice, Pilorz and Steinlechner found similar fecundity as in wild type in young adult, but there was lower reproductive success because of the low number of successfully delivered offspring in middle-aged mice.[68] On the other hand, mice deficient in Cry1 or Cry2 have accelerated age-related decline in fertility, as judged by the pregnancy rates in comparison with age-matched wild-type mice, but it was rescued by the adjustment of the light–dark cycles to match with the endogenous circadian rhythms.[69]

The effects of environmental perturbations and consequent disruption of circadian clock on reproductive function have tested as well. Pregnant female mice were exposed to a 6-hour advance or delay of the light/dark cycle every 5 or 6 days.[70] Both phase advances and delays were associated with a reduction in pregnancies carried to term, even though the reduction was more prominent in relation to phase advances (78%) than delays (50%).

Biological rhythms of fertility: human studies

Recently, most of the human studies on biological rhythms of fertility have examined the consequences of rhythm disruption due to social cues such as shift work or jet lag. Earlier, before the era of hormonal contraception and assisted reproduction technology, human data suggest that there was a seasonal effect on fertility.[71] In addition, a limited number of studies have focused on the relationship between clock gene polymorphisms or chronotype and reproductive function in women and on the circulating levels of KISS in relation to reproduction.

A number of studies performed on shift workers such as flight attendants and nurses have suggested an association of irregular work schedules or night shifts with altered menstrual and reproductive functions. Increased risks of menstrual irregularities, spontaneous abortion, premature birth, and low birth weight have been reported.[72–78] In a survey carried out in the USA in 1978, shift work was associated with longer menstrual cycles and menstrual disturbances in nurses.[79] A few years later, a big Japanese survey found more menstrual irregularity and pain and a lower pregnancy rate in women working during the night shifts than those during the day shifts.[76] Furthermore, among 726 women involved in manufacturing, the menstrual irregularity and longer cycles were associated with a variable schedule for work during the day, but not with day shift work which probably guaranteed a more regular rhythm for working hours.[80] In a multicenter study,[81] Bisanti et al reported an association of shift work with subfecundity, ie, with unprotected intercourses during >9.5 months but not with menstrual cycle length or irregularity. A Swedish study on 807 hospital workers found that women who worked during the evening shifts had an increased risk of having low-birth-weight infants compared with those working only during the day, whereas women working only in the night shifts did not have an increased risk of miscarriage.[75] Labyak et al found shift work to be associated with menstrual cycle irregularities and, to a lesser extent, infertility.[82] In detail, they surveyed 68 nurses aged 22–39 years, working in shifts on average for 3.3 years; 36 (53%) of them reported menstrual changes, ie, variations in the duration of menstrual cycle and bleeding, variations in the amount of menstrual flow, and increased menstrual pain during shift work. In addition, three (4%) of them reported infertility when working in shift work, and of the nine reported miscarriages, five occurred during shift work. Recently, Lawson et al analyzed the menstrual characteristics of 71,077 nurses participating in a national cohort study.[83] They did not study the effects of permanent night work but found associations of working rotating night shifts with irregular menstrual cycles and showed that the risk for menstrual irregularity increased with the higher number of months worked in rotating shift work (13% increase per every 12 months). Rotating shift work was associated with an extreme duration of the cycle (either short or long), and the risk of extremely long cycles increased with the increased number of months worked in rotating shift work (by 25% per every 12 months).

However, there are in contrast a number of studies that have failed to find a clear association between shift work and altered fertility in women.[83–86] For example, results from the Danish National Birth Cohort, which included 21,438 pregnant women either daytime (82%) or shift workers, suggest that rotating shift work, either with or without night shift, is not associated with reduced fecundity. It is of note here that workers having fixed evening or fixed night shifts had longer time to pregnancy and lower fecundity odds than daytime workers. The authors suggest pregnancy planning bias, rather than biological (eg, circadian) effects as a possible explanation for these differences.[86]

A number of studies have also been carried out among flight attendants, who are repeatedly exposed to jet lag and consequent circadian rhythm disruption. Among 418 flight attendants who had one or more pregnancies during the study period, Cone et al found spontaneous abortion in 15% that is comparable with the rate of miscarriage on population level.[85] However, spontaneous abortions were more common among flight attendants who had worked more flight hours during their pregnancy. Similarly, a registered-based study of Finnish flight attendants found similar rates of spontaneous abortions as in the general population, even though women who actively worked as flight attendants during the early pregnancy had slightly higher risk of spontaneous abortion compared with those who did not.[84] Moreover, a study on 1995 Italian flight attendants found no significant differences in the rates of spontaneous abortions or in the duration of menstrual bleeding between women who were actively in service and those who were not; however, women in service were more likely to report menstrual irregularity than those not in service. Additionally, 62% of the women reported menstrual disorders, eg, menstrual pain, heavy bleeding, and periods of amenorrhea, while working as flight attendants, and 21% reported lifetime infertility problems.[87] The aforementioned reports should be treated with caution. A number of physical and chemical factors other than circadian rhythm disruption, eg, exposure to cosmic ionizing radiations, cabin air quality, and psychological distress, may contribute to the results of altered reproductive function in female flight attendants.

A Finnish population-based genetic study provides support for the role of clock gene polymorphisms in human fertility.[88] In detail, the authors investigated different polymorphisms of the clock genes *CLOCK*, *BMAL1*, *BMAL2*, and *NPAS2* in 99 women who participated in a representative nationwide population-based health examination study. Genetic variants in these clock genes were analyzed in relation to reproductive health characteristics such as regularity of the menstrual cycle, the number of pregnancies and miscarriages, and infertility. They found a linkage between a genetic variant in the *BMAL1* gene (the TT genotype by rs2278749) and a higher number of pregnancies and miscarriages. On the other hand, a genetic variant in the *NPAS2* gene (the T^+ status by rs11673746) was associated with a lower number of miscarriages.

Behavioral phenotypes deriving from individual differences in the timing of circadian physiological functions (eg, sleep–wakefulness cycle, hormone secretion) are called chronotypes. On the basis of these phenotypes, three chronotypes can be identified, ie, morning (subjects who go to bed and wake up early and perform at their best during the morning), evening (subjects who go to bed and wake up late and perform at their best in the evening), or intermediate (neither morning nor evening). A relatively small number of studies suggest a relationship between eveningness and more menstrual pain and a shorter duration of menses.[89,90] We have previously analyzed the associations between chronotype and reproductive features in 2,672 female participants of the National FINRISK Survey 2007. We found a longer duration of menstrual cycle among evening chronotypes than among morning and intermediate chronotypes. Additionally, intermediate chronotypes had a significantly longer duration of menstrual bleeding as well as higher odds for difficulties in getting pregnant, suggesting an association between the chronotype and reproductive functions in women.[91]

The human placenta produces KISS.[92] The plasma levels of KISS increase significantly during pregnancy, while obstetric complications such as preeclampsia seem to be associated with lower KISS plasma concentrations.[93] Jayasena et al found significantly higher plasma and urine (but not saliva) levels of KISS in 49 pregnant women (gestational age of 34±0.6 weeks) as compared with 50 healthy nonpregnant women.[94] On the other hand, when analyzing plasma KISS levels in 993 pregnant women, the authors found an association between lower levels of KISS and higher risk of miscarriage.[95] Additionally, it has been demonstrated that KISS can induce LH surge and egg maturation in women.[96]

The LH surge that lasts for a day or two is usually initiated between midnight and 8 am in women. In order to determine the time of onset of the LH surge, Cahill et al collected repeated LH level measurements at 4-hour intervals, from day 9 of the ovarian cycle in 35 women younger than 40 years and with normal ovulatory cycles in a total of 155 cycles.[97] They found that the onset of the LH surge occurred mostly (85%) during the night hours between 12 am and 8 am Similarly, Kerdelhué et al examined blood samples of 19 women,

which were taken at 4-hour intervals during days 7–10 of the menstrual cycle.[98] The LH surge onset occurred in the early morning in most of the cases, ie, at 4 am in 20% of the cases or at 8 am in 80% of the cases.

Interestingly, the exposure to visible light via the eyes influences the reproductive events in humans, and therefore the correctly timed light exposures might support reproduction if the effect of light is transmitted from the retina to the SCN and other key areas in the brain. Infertility is more common in blind women.[35] Furthermore, long and irregular menstrual cycles can be normalized by ambient light exposures administered at night during the days 13–17 of the menstrual cycle.[36] This original report was supported and extended by findings that the menstrual cycle was shortened in 38 patients with winter depression after the daily exposure to light for 1 week as started between the days 1 and 14 of the menstrual cycle[99] and that exposure to sunshine 2 days or 3 days before the ovulation appears to shorten the menstrual cycle.[100] Moreover, among women with lengthened menstrual cycles, the ovulation was promoted, the follicle size was increased, and the circulating levels of prolactin, LH, and FSH were increased by the daily exposure to bright light for 1 week between the days 7 and 14 of the menstrual cycle.[101] The effect of light on FSH secretion appears to be direct, mildly stimulating, and transient.[102]

The circadian clocks in humans seem to be similar to those of other species in their response to light exposures. An electrical stimulus resets the phase of a spontaneously rhythmic neuron, and single clock neurons in the SCN whose functions are guided by clock genes and their protein products synchronize their phase to produce a coordinated time-giving signal for circadian rhythmicity.[103] A stimulus of visible light of a critical strength that is applied to the eyes at a critical circadian phase did reset the human circadian clock, as measured with core body temperature, close to its singularity, ie, a position with no phase at which the amplitude of circadian oscillation is zero.[104] The mechanistic explanation to this universal property of the circadian clocks was finally provided with experiments, where it was shown that critically timed light pulses drove cellular clocks into their singularity and that the desynchronization of individual cellular clocks underlay singularity.[105]

Currently, there are, however, no data on the clock genes and their protein products from normal human reproductive tissue, apart from in connection to cancer examinations. Instead, there are some human data on the clock genes as they were expressed in peripheral tissues in response to perturbations that might reduce fertility. Mistimed sleep such as it occurs in shift work or due to jet lag did affect the molecular regulators of circadian rhythmicity and among others the clock genes *CLOCK* and *BMAL1*.[106] Further, shift work broadly altered the clock gene expression levels and increased the circulating level of 17-β-estradiol, as measured in the morning during the early follicular phase of the menstrual cycle among rotating-shift nurses.[107] However, these findings are conflicting, as there are negative studies as well,[108,109] possibly due to differences in the details for study design.[110]

Conclusion

The seasonal and circadian rhythms continue to regulate many biological functions in animals, including humans. As for other processes, the rhythmicity of reproduction and fertility is regulated through a complex interaction between the environmental stimuli and the endogenous central as well as peripheral oscillators. Animal studies have clearly demonstrated the role of core clock genes and clock-controlled genes in regulating the timing of the ovarian cycle. Only a few studies have been carried out to infer the role of circadian rhythms in human reproduction. Further research that will focus on the role of the HPO axis, the circadian mechanisms of action, and consequences of the circadian disruption in reproduction and fertility is warranted.

Disclosure

The authors report no conflicts of interest in this work.

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