Review Article

Deregulated Brain's Central Clock Management on Sleep-Wake Behavior in Women With Polycystic Ovary Syndrome: Melatonin & Sleep Pattern

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Abstract

The aim of this narrative review is to investigate the reciprocal correlation between melatonin through the brain's central clock management on sleep-wake behavior in women with polycystic ovary syndrome (PCOS). Biological clocks are genetically programmed physiological systems that permit organisms to live in harmony with natural rhythms. The most important function of a biological clock is to regulate overt circadian biological rhythms. Circadian rhythms orchestrate the body's rhythmic physiologic functions like sleep-wake and menstruation cycle. Stress hormones, beta-endorphins, and melatonin which can easily affect the woman's reproductive system. For example, amplitude changes in the luteal phase are one of the results of menstrual-related disorders that occur through this circadian fluctuation. Many reports indicate that levels of melatonin and stress hormones are altered in women with PCOS. The melatonin metabolites are significantly raised in the level of night-time urinary in women with PCOS, which is associated with a significant reduction of sleep quality compared to normal women. The result of this narrative review showed the circadian rhythm as a normal coordinated function is a regulator of the natural structure of sleep-wake architecture. Disruption of this natural pattern can lead to phasic activation of the HPA axis, which increases the continuation of circadian activation; which there is in women with PCOS.

Keywords: Circadian Rhythms; Melatonin; Sleep-Wake Architecture; Sleep Quality; Polycystic Ovary Syndrome (PCOS)

Introduction

1- Circadian oscillators

Circadian rhythms are cycles of 24-hour physiological and behavioral functions which are synchronized with environmental cycles, like sleep-wake. The suprachiasmatic nucleus (SCN) of the hypothalamus is the master circadian clock, with the circadian rhythms in clock gene expression have various roles, like emotional, motivation, learning, releasing of hormones, and feeding (1). Recent studies show that a set of cell clock genes (pacemakers), known as multiple clocks throughout the body, can synchronize the body's circadian timer (2). This complex innate timing system as a biological clock in the brain can enable living organisms to manage with repetitive changes. The

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genetic programming of this clock is for physiological systems with natural rhythms include the sleep-wake cycle and in peripheral include: control of the reproduction behaviors (3), and many features of metabolism activities like glucose homeostasis (4, 5), lipogenesis (6), and xenobiotic detoxification (7).

Brain biological clock: In 1990, the first report was about the molecular clock mechanisms in the adrenal gland for endogenous rhythmic activity (8).

The dominant pacemakers of hypothalamic suprachiasmatic nuclei (SCN) are regulators of the daily expression for vital homeostatic functions (3). These regulations by circadian oscillations are produced by a set of genes forming in a feedback loop of the transcriptional autoregulatory system. In mammals, this set include, Clock, Bmal1, Per1, Per2, Cry1, and Cry2 (9).

Brain biological clock & Adrenal glands: the reports of the rhythmic expression of the clock gene in adrenal glands, as the first organ for circadian rhythmicity, show that the output of the circadian adrenal has a critical role in synchronizing between interior and exterior environment in seasonal alterations, shift work, or fast travel among many time zones (10, 11, 12). This reciprocal communication between SCN master pacemakers in the hypothalamus and adrenal glands is prepared through the circadian release of adrenocorticotrophic hormone (ACTH) (13).

Brain biological clock & Cortisol: Cortisol is a master hormone with a very complex role in the circadian rhythm which can influence mental, emotional, and physical strength. Cortisol increases after wakening in the morning (50%), which this elevation occurs on the late-night before awakening. The amplitude of cortisol awakening response (CAR) is partly determined by many factors of circadian adrenal. The amplitude of cortisol awakening response (CAR) is partly determined by many factors of circadian adrenal. The phasic activation of the HPA axis by awakening can be an announcement of the continuing circadian activation. Wilhelm et al. in 2007 proposed that the peak of cortisol levels in the CAR has not related to the night levels of cortisol, and modulation of the CAR was followed by the night-time state of activity rate of the HPA axis and is independent of the mean cortisol levels in the following morning period (14, 15). Immediately after wakening, the decrease in the level of cortisol can be connected to poor sleep quality in patients with primary insomnia (16).

Brain biological clock is synchronized by neurohormones: The adrenergic locus coeruleus (LC) nucleus as a small core of the brain is another potential factor for awakening response (17). The SCN as central clock could entrain the peripheral oscillators in the adrenal gland via the two pathways introduced in the foregoing: 1) the humoral pathway of the HPA-axis, and 2) the neural pathway of the autonomic nervous system (ANS). Studies on the hypophysectomized rats show that the adrenal oscillator acts independently of humoral SCN signaling via the pituitary gland (18). The HPA axis is under the regulatory control of circadian oscillators, yielding a distinct 24-h rhythm of cortisol secretion from the adrenal cortex (19).

Zubieta et al., in 2003 showed that the induction of negative mood states can be related to a significant deactivation of μ-opioid that has a direct relationship between the rate of euphoria and the opioid displacement. The reduction of opioid activity is the result of over-activity in the sympathetic nervous system (SNS) (20, 21). Beta-endorphin in the brain can stimulate adrenocorticotropic releasing hormone (ACTH) and noradrenaline (NA) via opiate receptor. Grossman et al. showed that naloxone administration (16mg) to healthy men can significantly increase plasma cortisol level which can inhibit with the alpha-1 antagonist. Therefore, they suggested that this opiate inhibition of the pituitary-adrenal axis is mediated through the noradrenergic pathway (22, 23). Stress hormones, Beta-endorphin, and melatonin are involved in the process of the sleep-wake cycle. Most neurons which are located in the arcuate nucleus (ARH) of the basal hypothalamus can produce beta-endorphin beside the third ventricle, and smaller group neurons in the caudal brainstem. Herbert in 1993 reported that activation of the opiate system can destroy reproduction physiology, and zangeneh et al. in 2011 reported that there is an interaction between the sympathetic nervous system and opioids in rat modeling of PCOS (23). Beta-endorphin reduces sympathetic tone (24), and many studies confirm hyperactivity of the SNAS can be the basis of ovarian PCOS. For example, exercise can increase circulating beta-endorphin by depending on the type exercise and its intensity (25, 26). Beta-endorphin decreases the sympathetic tone, therefore can be a significant factor for the lifestyle of women with PCOS. B-endorphins are mostly involved in weakening acute stress responses, but not essentially in the management of

long (or chronic) stressors (25). The communication networks with the feedback and feedforward loops in this synchronization are very complex, and lifestyle behaviors' over a long-time can disrupt this significant communication.

2- Melatonin

Melatonin as an indolamine hormone (N-acetyl-5-methoxytrypamine) was first recognized in the 1950s. It is the important hormone for sending rhythmic information of photoperiodic signaling from the environs to the organism. The main role of melatonin is the synchronization of daily and annual physiological rhythms to environments. Melatonin has a modulator role in the activity of pituitary cells. It is an important regulator for direct and indirect production and release of different hormones in the anterior pituitary gland at the demand of organism during the day, during different seasons, and at different stages of life. Therefore, the action of melatonin in the brain centers is similar to its action in the tissue, which is associated with positive and negative feedback (27). Melatonin has an inhibitory effect on the pituitary gland with input to the circadian-pacemaker of the suprachiasmatic nucleus (SCN) of the hypothalamus (28). In tissue, mitochondria seem to be a significant site for the production of melatonin in cells. In addition, follicular cells, oocytes, and cytotrophoblasts are also other sites for its synthetization (29).

Melatonin receptors (MTR): MTR are G-protein transmembrane receptors include melatonin receptor 1 (MTR1a, b, c, d; MTNR1A) (30) and MTR2; MTNR1B (31). Studies on the MT1 / MT2 receptor knockout mice indicates that MT1 receptors have activator role on the regulation of REM sleep phase or rapid eye movement, whereas MT2 receptors selectively improve non-REM sleep phase. Studies have shown that MT1 receptors are distinct from MT2 receptors. MT1 localization is in the locus coeruleus and lateral hypothalamus (REM areas) whereas the MT2 localization is in the reticular thalamus (NREM area) (32).

Melatonin and sleep phases: Mammals sleep in a rhythmic manner has two separate phases including rapid eye movement (REM) and non-REM (NREM). REM sleep with a short duration is associated with the augmented sympathetic tone, whereas NREM duration is longer and has the opposite role. The meta-analysis of melatonin shows that the soporific effect of melatonin is related to falling asleep, and has no effect on the quality and retention of sleep (33, 34). Inadequate sleep can be a very important factor in reducing the mental and physical health of people. Studies have shown that the changed function of the HPA axis might reason for this dependency.

Melatonin & HPA axis: The anterior pituitary endocrine cells are a good target for melatonin' s physiological behaviors such as growth, puberty, seasonal sexual maturation, metabolism, and stress. These endocrine cells are mostly controlled by two brain signaling centers: preoptic and hypothalamic areas, which are integrators for nervous and hormonal signals from different origins (35). These two brain areas have many melatonin binding sites in rodents and ruminants (36).

Neuroprotective effect of Melatonin (anti-oxidant properties): Despite the mechanism of melatonin binding at the receptors, melatonin also has a non-receptor-mediated reaction (Figure 1) (37). Melatonin is known as a powerful antioxidant with a direct scavenging effect on free radicals. It can activate a number of inhibitory mechanisms such as transcriptional stimulation and the activity of antioxidant enzymes and binding to intermediate metals to prevent the formation of hydroxyl radicals (38). Recent developments show that impaired circadian control of melatonin secretion plays an important role in age-related sleep disorders, Alzheimer's disease, and other progressive neuronal disorders. Evidence shows that melatonin through the anti-oxidant properties can be a potential neuroprotective hormone. A meta-analysis and review systemic have suggested that using of the supplementary melatonin can raise the total antioxidant capability (TAC), and an intake of melatonin has a significant impact on improving oxidative stress parameters (39). Many studies show that melatonin is the best candidate for protection against the destructive effects of oxidative stress (OS) (40).

Melatonin plays an important role in maintaining the balance of oxidants/antioxidants in tissues and can also affect cell damage with its anti-apoptotic effect (41). The anti-apoptotic effect of melatonin is achieved by stimulating antioxidant enzymes and inhibiting lipid peroxidation for the defense of cells against the degradation effects of oxidative stress (42). Morvaridzadeh et al. in 2019 showed that melatonin is a strong scavenger for free radicals and therefore it can be a potent protector in the folliculogenesis process during the oocyte maturation (43).

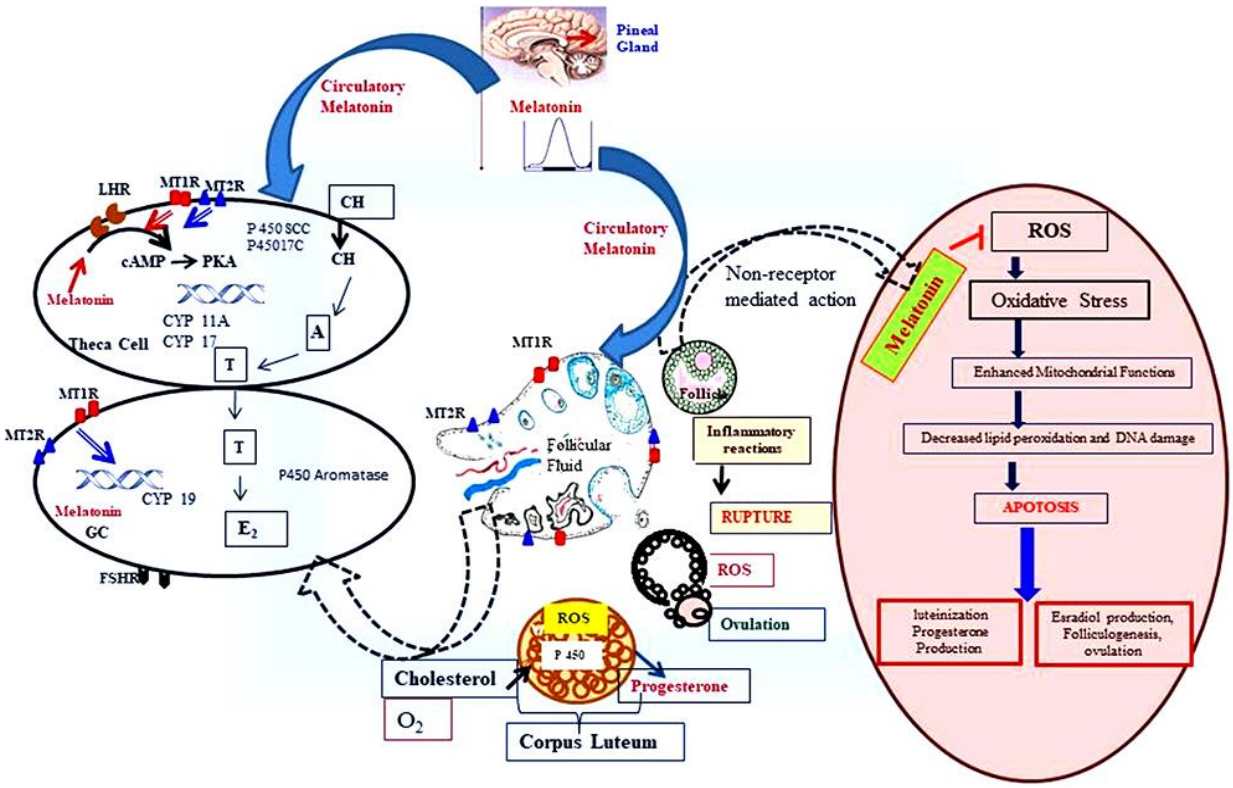

Figure 1: Presentation of the receptor and non-receptor mediated pathways for melatonin in the female reproductive system. By reuptake of melatonin in the granulose and theca cells, melatonin enters to follicular fluid for stimulation of the LH, FSH mRNA expression through binding of MT1R and MT2R for increasing and regulating steroidogenic enzyme activities. After follicular rupture, the ROS generation occurs by the inflammatory reaction in ovulation and steroidogenesis in the corpus luteum because of inflammatory reaction. Therefore, circulatory melatonin is an essential hormone for maintaining the balance between ROS generation and antioxidative enzymes for supporting maturity in the ovum (37).

3- Polycystic ovary syndrome (PCOS)

PCOS as a dominant hormonal disorder is common in the reproductive-aged women. PCOS is related with reproductive, endocrine, and metabolic abnormalities with a prevalence of 15-20% (44). Women with PCOS are at higher risk for infertility, endometrial dysplasia, and cancer with malignant ovarian tumors, pregnancy problems such as preterm delivery, birth with low weight and eclampsia. Cardiovascular disease and diabetes type 2 are the complex endocrine–metabolic interactions in women with PCOS (45). Although many studies have been performed on polycystic ovaries, the cause is still unknown.

Polycystic ovary syndrome & quality of sleep: The menstrual cycle situation and menstrual-related disorders must be considered when the women have complaints about their sleep. In 2015, Moran et al reported that sleep disorders in women with PCOS are almost twice as common as in healthy women of the same age. This finding highlights the importance of assessing and managing sleep and mental health problems in PCO women with quality of life (46). But, Hachul et al, 2019 reported that PCOS damages subjective and objective sleep quality, which is due to the reduction of REM sleep time, and hyperandrogenism have no effect on the sleep-related parameters. Therefore, they assume that women's sleep is mainly affected by obesity (47). Adult and adolescent women with PCOS are recognized to have abnormalities in sleep construction. In a polysomnography study, the REM and non-REM durations of sleep in women with PCOS were significantly reduced compared to healthy age-matched and non-obese control women (48). A study with a questionnaire showed that sleep delay in obese women with PCOS is more than non-obese women (49). The incidence of sleep problems appears to be increased in women with PCOS. Even though most studies of obese women with PCOS have focused on obstructive sleep apnea (OSA), which is common in

these women (50). Our findings 2016 confirmed this increasing sleep latency in non-obese women with PCO by the use of questionnaires (51). Sleep disorders are associated with PCOS, and in a meta-analysis, Helvaci et al. showed that adult women with PCOS are at higher risk (9.74 times) for OSA compared to health women with similar age (52). Animal model studies and human reports of SNS hyperactivity confirm this syndrome because insulin resistance and related metabolic effects, sleep disorders, and OSA are associated with sympathetic nervous system hyperactivity (Figure 2).

PCOS & melatonin: PCOS is a reproductive-metabolic disorder, and melatonin plays a modulation role in reproductive-metabolic, immunology, and anti-oxidation processes (53). The regulatory role of melatonin in the reproductive physiology of seasonal and photoperiod has been recognized. This regulatory role is done at the level of the hypothalamic-pituitary-gonadal (HPG) axis for gonadotropin-releasing hormone (GnRH) secretion and then regulates LH and FSH release (54). Tamura et al in 2009 reported that the intra-follicular level of melatonin is lower in women with PCOS compared with healthy women (55). Jain et al. in 2013 showed that the serum level of night-time melatonin in women with PCOS is higher than the control group (56), and zangeneh et al in 2014 reported that melatonin level in women with PCOS is lower in the daily in compared to control group (57). Spinedi and Cardinali study concluded that these alterations can be significantly responsible for the reduction of oocyte quality and anovulation in these women (58). In the in-vitro study, Pacchiarotti et al showed that melatonin and myoinositol as a melatonin supplement could significantly induce an increase in the oocyte quality and embryo development in women with PCOS compared to the control group (myoinositol alone) who were candidates for IVF (59). Melatonin is detectable in the pre-ovulatory follicular fluid, and its level is remarkably higher than its serum level (60). The pre-ovulatory follicles have high levels of melatonin compared to small immature follicles; which may be produced in granulosa and oocyte cells (60). There is ample evidence that the concentration of melatonin in the luteal phase is significantly higher than in the follicular phase of the human menstrual cycle (60, 61). Melatonin directly stimulates the production of progesterone by granulosa cells or luteal cells and might act at the ovary level to regulate luteal function (62, 63). Therefore, melatonin as a sleep hormone can be a direct role in imbalanced hormones and sleep disorders in women with PCOS. Therefore, targeted screening and management of sleep disorders in PCOS is essential.

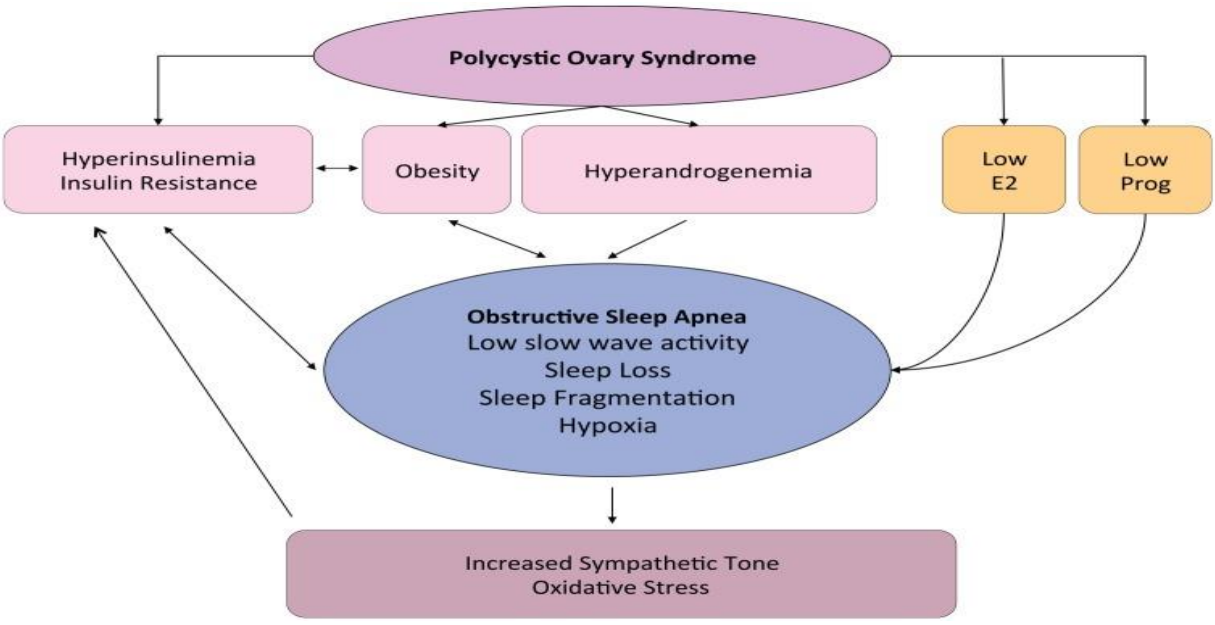

Figure 2: PCOS is associated with the hyperactivity of the ovarian sympathetic nervous system. Therefore it is related to irregular menstruation, adiposity, insulin resistance, and hyperandrogenism. These abnormalities predispose to the development of sleep disorders and OSA in women with PCOS.

Discussion

Melatonin is introduced by the special effects on the mammals' sleep and reproductive system. Melatonin has a wide-ranging on the female reproductive system and is the trigger of its rhythmic release at puberty time. This rhythmic releasing continues during fertile female life, by modulating the varied ovarian functions include: folliculogenesis, steroidogenesis, quality of oocyte, ovulation, and luteal function. The gene expression of sex steroid receptors for the ovarian steroidogenesis in the thecal cells and oocytes is very important. For example, folliculogenesis is a complicated process caused by autocrine, paracrine, and endocrine signaling pathways, which has critically dependence on circulating levels of FSH. The human follicular fluid (FF) during pre-ovulatory period has a higher melatonin concentration than in serum. It is begun with the primordial follicles and progress into the primary, prenatal, and antral stages, for reaching to the pre-ovulatory stage. In the pre-ovulatory period, the cumulus-oocyte complex (COC) expands for maturation of the meiotic phase and enables the capability (64). Steroidogenesis begins with employment of antral follicles which is described by the induction of gene expression of mRNAs encoding of steroidogenic enzymes, gonadotropin receptors, and local regulatory factors. Research findings show that the role of melatonin in the steroidogenesis occurs at the molecular level, particularly the mRNA expression of the two genes CYP 11a and CYP17, which are rate-limiting steps in this biosynthesis pathway. In the pinealectomy rat, melatonin treatment can effect on the CYP17 expression and steroidogenesis process (65). Picinato et al. 2008 suggested that melatonin (0.1 mM) can activate the two intracellular signaling pathways: 1) the PI3K/AKT, by induction of insulin like growth factors-I (IGF-I) receptor which is involved for the cell metabolism, and 2) MEK/ERKs (ERK signaling cascade is a central MAPK pathway) that join in cell proliferation, development, and differentiation (66). The IGF-I and IGF-II belongs to the insulin receptor family which can stimulate DNA synthesis and estradiol (E2) and progesterone secretion by human granulosa and granulosa-luteal cells (67). These findings show the modulation role of melatonin at the level of M1, M2 receptors and its powerful antioxidant effect (scavenger) on follicular-steroid production which depends on the cell type (granulosa or theca cells), and duration of action (fast or long-term response). This review considers melatonin as a specific hormone that acts in the field of its biological time. To counteract these timeline effects, melatonin has developed unique methods with or without a receptor (Figure 1). The findings of animal and human studies show that melatonin can improve oocyte quality, and increase success in-vitro fertilization (IVF) (68). The role of melatonin in maintaining oocyte quality can be attributed to its antioxidant action, because oxidative stress, due to ROS generation during the follicle rupture, may be a cause of poor oocytes quality (69). This antioxidant action facilitates the apoptosis process and causes to decline of cell membrane lipids and destroys DNA etc. The balance between the production of ROS and its destruction by melatonin (as a powerful scavenger) plays an important role from the oocyte maturity until fertility (70).

The important questions include:

1- Can the vital-physiological role of melatonin be applicable in pharmacological treatment?
2- Is melatonin sufficient as a drug to protect oocytes and their surrounding nutrient cells from damage?
3- Can melatonin suffice as a sleep-trigger drug in sleep disorders in healthy women or with PCOS?
4- Can melatonin therapy solve both problems by a uniform dose in women with PCOS?

Melatonin administration (5 mg/kg body weight) increases superoxide dismutase (SOD) activity, its serum level (1 nM), and induction gene expression of all three antioxidant enzymes (i.e., Cu, Zn-SOD, Mn-SOD, and GPx) (71, 72). According to the above reports, melatonin can certainly activate antioxidant enzymes and increase their gene expression. Thus, these data may suggest that melatonin can be the choice drug for improving oocyte quality in women with PCOS, and poor ovarian response who are unable to conceive due to low oocyte quality. Xiao et al in 2019 reported that estrogen (E2) has a significant role in regulating of the MT1 and MT2 expression as well as melatonin synthesis in sheep cumulus-oocyte complex through the estrogen receptor signaling (73). The aim of this review was investigation the physiological role of melatonin in women with PCOS. In women with PCOS, HPA and hypothalamus-pituitary-ovarian (HPO) axes associate with the PCOS endocrine dysfunction, such as hyperandrogenism and metabolic abnormalities include insulin resistance, obesity, type II diabetes, dyslipidemia. Research has shown that there is a strong correlation between oxidative stress and the development of insulin resistance and even late-stage

diabetes. Oxidative stress (OS) is a metabolic disorder that results in an increase in the production of reactive oxygen species (ROS) and the body's antioxidant defense system. Recent genomic studies have also suggested that the cause of the pathogenesis of type2 diabetes is disruption of melatonin receptor signaling pathways (74).

Conclusion

This narrative review focuses on circadian oscillators in women with PCOS. Naturally, this study relates to the rhythmic behaviors of women, including menstruation, the secretory rhythm of sex hormones and LH surge in the process of two axes homeostasis (HPA and HPO) in female reproduction system; which are impaired in the women with PCOS. Exposure to light can disrupt melatonin release late at night (female staff on the night shift), so during this time, light can be caused asynchronous and suppression of the circadian rhythms by a changed melatonin releasing pattern. Melatonin is a dark hormone instead of a sleep hormone. Melatonin is an essential endogenous factor for the body's circadian oscillators, and external factors including lifestyle, occupation, and social-cultural factors can all factors contribute to this inconsistency. A lifestyle change in women with PCOS is the best and least expensive option to address this incongruity.

Conflict of Interests

The author has no conflict of interest with any other parties.

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