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The Female Reproductive System: an Overview of The Effects Of Melatonin

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Abstract: The hormone melatonin is closely related to vertebrate reproduction, especially in the context of seasonal reproduction. This relationship is due to the fact that melatonin is secreted from the pineal gland into the peripheral circulation only during the night, and the duration of secretion reflects the length of the night. While melatonin secretion increases with the prolongation of the nights in the winter months, it decreases with the shortening of the nights in the summer months. This mechanism is critical in the adaptation of reproductive cycles to environmental conditions in many vertebrates. Recent research has revealed that melatonin regulates reproductive functions through MT1 and MT2 receptors and affects female infertility. Furthermore, melatonin has a strong free radical scavenging property and plays a critical role in reducing oxidative stress. Melatonin can also improve egg quality. Given these far-reaching effects, melatonin is important in females. The purpose of this review is to summarize the current understanding of the role of melatonin and its receptors.

I. Introduction

Melatonin is known as *N-acetyl-5-methoxytryptamine*, known as the tryptophan derivative secreted by the pineal gland in vertebrates (Siu et al., 2006). From past to present, melatonin has been considered as an endocrine hormone secreted from the pineal gland and subsequently acting on G-protein-dependent melatonin receptors in adults and target tissues of the fetus (Cecon etal., 2018). This molecule is found in many systems such as the reproductive system, gastrointestinal tract, and nervous system, and it has recently been reported that this molecule is synthesized in trace amounts in various animal cells and tissues (Reiter et al., 2013; Acuna et al., 2014). It should also be noted that melatonin may have paracrine and autocrine effects independent of its specific receptors (Manchester et al., 2007). Melatonin interacts with a large number of cellular proteins such as various enzymes, signaling molecules, channel systems. For example, it goes to bile, brain fluid and amniotic fluid by using various pathways, as well as taking part in neuroendocrine, angiogenesis functions and physiological processes (Tamura et al., 2014; Liu etal., 2019). Various studies have identified melatonin activity as a protective agent in situations such as oxidative stress or in programmed cell death processes (Rodriguez et al., 2013). Melatonin has also been proven to have a regulatory role in the mechanism of cardiovascular, immune and reproductive system, and it has been stated that melatonin is needed to protect from oxidative stress in the reproductive system (Ruder et al., 2009). It has been discovered that melatonin and melatonin receptors

can regulate seasonal reproduction in mammals through the hypothalamus-pituitary-gonadal axis (Lincoln and Clarke, 1994). In a study conducted by Woo et al. (2001), melatonin receptors were shown to have a direct effect on gonads in the female and male reproductive system. They also stated that there are 2 subtypes of melatonin receptors MT1 and MT2 in human luteal granulosa cells and ovarian cells. Therefore, melatonin may affect female reproductive system organs such as ovary and uterus through melatonin receptors. It can affect reproductive function by regulating the synthesis and secretion of gonodal hormones (Sirotkin et al., 1997; Reiter, 1998). Nakamura (2003) reported that follicular fluid in human ovarian tissue contains high concentrations of melatonin. In the same study, it was also stated that the melatonin concentration in the antrum of the Graaf follicles was very high. Considering the biological function of melatonin, its relationships with circadian rhythm, endocrine functions, and reproduction in general have been of interest for the use of melatonin. Recent studies have shown that organelles are frequently involved in the synthesis of melatonin. Melatonin, especially synthesized by mitochondria, is known to help the physiological processes of the cell (Soufu et al., 2017). The human body can be exposed to varying concentrations of melatonin from implantation to death. Because melatonin is functionally in communication with various signaling pathways from the embryo period to adulthood (Olcese, 2020).

Melatonin has an important role in regulating the menstrual cycle in women with the release of reproductive hormones. In particular, it has an effect on the gonodal axis of the hypothalamus. It controls the secretion of hormones such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Rai and Gosh., 2020). In addition, studies have suggested that melatonin and melatonin receptors have a potential role in women receiving infertility treatment, and that melatonin supplementation in IVF treatments may increase egg quality (Genario and Morello, 2019). Many studies have presented evidence that falling estrogen hormone levels in women during menopause associated with estrogen hormone may be due to the relationship between changes in melatonin concentration and sleep disturbances (Genraio & Morello, 2019; Rai & Gosh, 2020).While melatonin has various effects on the female reproductive system, it should not be forgotten that excessive melatonin use or sudden decreases or increases in melatonin levels may disrupt hormonal balance. The current literature predicts that melatonin can regulate the neuroendocrine axis on reproductive biology in humans (Rai and Gosh., 2020). The aim of this study is to explore more comprehensive information about melatonin and the new horizon of reproductive system studies and to point out the modulatory function of melatonin, especially on the female reproductive system, and to set an example for future studies in this field. As a result, it is expected to shed light on the therapeutic potential of melatonin, which may be beneficial for improving human reproductive health and fertility rates.

I. HOW IS MELATONIN SYNTHESIZED?

The pineal hormone melatonin (N-acetyl-5-methocytryptamine) exhibits a rhythm produced by the pacemaker responsible for the circadian rhythm located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is actually synchronized for 24 hours by the light-dark cycle acting on the SCN (Reiter et al., 2011). Serum melatonin levels are low during the day and this concentration increases at night. This actually suggests that melatonin physiologically directly affects the overall circadian rhythm, including body temperature, endocrine rhythms, and sleep (Lopez-Canul et al., 2019). During melatonin synthesis, first, L-tryptophan is converted to serotonin, immediately followed by N-acetyl-5-hydroxytryptamine metabolized by serotonin N-acetyltransferase (AA-NAT). Finally, N-acetyl 5-HT is converted to melatonin by hydroxyindole-o-methyltransferase (Reiter, 1991). The induction of molecules such as 6-hydroxymelatonin (6(OH) melatonin) and 5-methoxytryptamine (5-MT) of the melatonin molecule causes the passage of metabolites that are not able to pass through the cell membrane. They also have the ability to act as antioxidants and pro-oxidants (Janjetovic et al., 2017; Kleszczyński et al., 2018). Melatonin connects with two G-protein-associated receptors, MT1 and MT2. It cooperates with melatonin as a detoxification enzyme in MT3, the human quinine reductase 2 receptor (Benitez-King and Anton, 1993). Melatonin, which has an effect on the circadian system, is known to improve sleep disorders in relation to sleep patterns. Dopamine, a neuro modulatory molecule, can physiologically regulate light adaptation together with melatonin. In a study conducted by Eryılmaz et al. (2011), it was stated

that 3 mg melatonin per day did not improve sleep problems. Melatonin receptor 1A (MTNR1A), also known as MT1, is frequently recommended as a key target gene that plays an important role in regulating photoperiod-related seasonality (Notter and Coccet, 2005). When there is no light and in the appropriate circadian phase, inhibition on the pineal gland is removed and melatonin begins to be secreted. However, disruptions in the circadian rhythm can suppress melatonin release. The pineal gland secretes melatonin into both the bloodstream through passive diffusion and the third ventricle of the brain through the pineal recess. In humans, melatonin synthesis occurs in the pineal gland and secreted melatonin spreads to all body tissues through the bloodstream (Pandi-Perumal et al., 2006; Hardeland et al., 2011).

II. Pineal Gland and Melatonin Biosynthesis

Melatonin is a small indolamine with a molecular weight of 232.3, which is secreted rhythmically, reaching its highest level during dark periods. Changes in peripheral illumination are transmitted to the central nervous system through the peripheral nerves, from where they affect the hormonal release of the pineal gland through multisinaptic neural connections. In mammals, the circadian photoreceptors of the retina sense light and dark signals and transmit them directly to the suprachiasmatic nucleus (SCN) via the Retino-Hypothalamic Tract (RHT). Neuronal projections starting from the CN travel along the medial forebrain bundle in the paraventricular nucleus (PVN) of the hypothalamus to the intermediolateral cell column of the spinal cord. Preganglionic fibers from here go to the upper cervical ganglia and contribute to the regulation of circadian rhythms (Rai and Gosh, 2020). Sympathetic postganglionic noradrenergic fibers from the upper cervical ganglia provide innervation to the pineal gland through the nervi conarii. Interruption of this pathway by SCN or PVN lesions or upper cervical ganglionectomy stops the synthesis of melatonin in the pineal gland. Melatonin production depends on a number of biochemical processes that are triggered by noradrenergic stimulation and take place in pinealocytes. In this process, N-acetyltransferase (NAT) activity constitutes a critical regulatory step of melatonin synthesis (Rai and Gosh, 2020). The rhythmic release of melatonin is regulated bycAMP-dependent transcriptional control mechanisms. The biosynthetic pathway of melatonin involves the hydroxylation and decarboxylation processes of tryptophan.Serotonin is acetylated by the rate-limiting enzyme NAT and then methylated to melatonin (5-methoxy-N-acetyltryptamine) in the pineal gland via hydroxy-indole-O-methyltransferase. After the synthesis is completed, melatonin is secreted into the blood and cerebrospinal fluid.

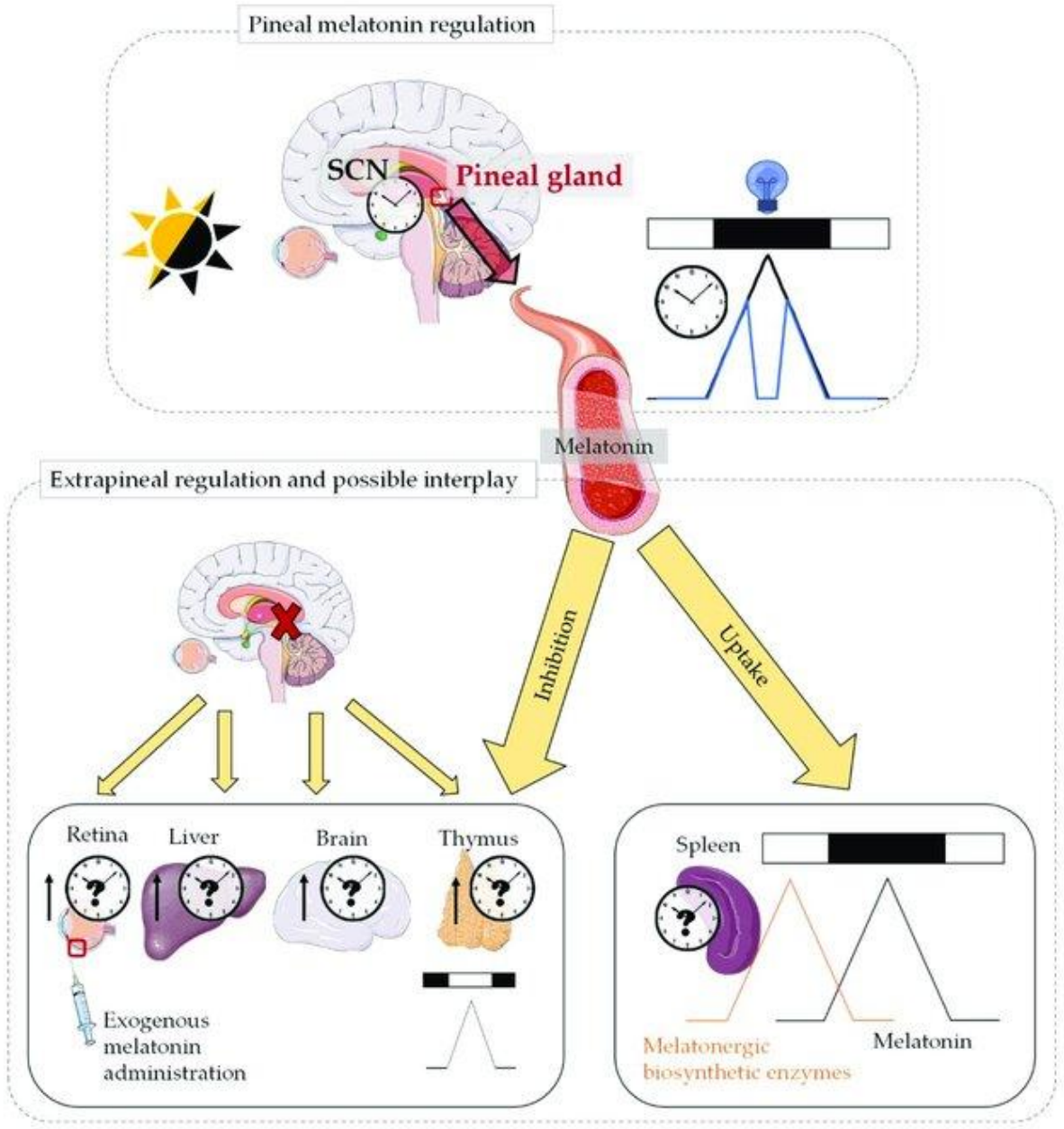

Figure 1. The regulation of pineal melatonin secretion (above), which is subjected to the circadian rhythm formed in suprachiasmatic nuclei(SCN), is driven by the light-dark cycle (night peak) and abruptly suppressed by light at night. Possible circadian regulation of extrapineal melatonin production in the retina, liver, brain, thymus, and spleen is shown below. A potential interaction with pineal melatonin is proposed (yellow arrows) (Bonmati Carion 2021).

III. Melatonin and the Female Reproductive System

Relationship Between Melatonin and Progesterone Hormone

Melatonin plays a critical role in the regulation of circadian rhythms associated with visual functions, reproductive activities, the cerebrovascular system, neuroendocrine and neuroimmune processes (Franklin et al.,

1997). Studies have shown that melatonin hormone plays a critical role in reproductive activities and blastocyst implantation in many mammalian species such as sheep, ferrets, horses, hamsters and rats. It also reports that the transfer of melatonin from the mother to the fetus, the daily photoperiod perceived by the mother during pregnancy or breastfeeding, is transferred to the fetus through the placenta or milk (Arend, 1995; Bishnupuri and Haldar, 2000). Reactive oxygen species (ROS) have a physiological role in ovulation. Apart from this, it has damaging effects on granulosa cells during the formation of lutein hormone. ROS can detect damaged cells, including apoptosis, cell nuclei, mitochondria, and plasma membrane (Wu, 2011). Luteal cells maintain a balance between ROS and antioxidants present in the follicle during ovulation because ROS can suppress the steroidogenic enzyme (Galono et al., 2013). Melatonin, on the other hand, supports progesterone production with its inhibitory effect on hydrogen peroxide ($H_2 O_2$) (Taketeni,2011). Tanabe et al. showed that melatonin inhibits mitochondrial dysfunction, lipid peroxidation, DNA damage and apoptosis in granulosa cells by reducing reactive oxygen species (ROS) (Tanabe et al., 2014). It also suggests the existence of another mechanism that melatonin can contribute to the developing functions of the reproductive system in connection with the role of the mitochondrial membrane in the steroidogenesis of granulosa cells (Arakane et al., 1998). Melatonin supports and protects oocytes by maintaining the integrity of granulosa cells in the follicle during ovulation (Tamura et al., 2014). About thirty years ago, Brzezinski et al. (1987) revealed that human preovulatory follicular fluid contains higher levels of melatonin than plasma levels of melatonin. Later studies reported that it changed inversely with day length and simultaneously with follicular progesterone (P4) levels and confirmed Brzezinski's studies (Roennberg et al., 1990; Yie et al., 1995). Nakamura et al. (2003), on the other hand, determined that larger preovulatory follicles had higher melatonin levels compared to smaller and immature follicles. In addition, observations that increasing oral melatonin doses significantly increased melatonin concentrations in the follicular fluid of female volunteers support this finding (Nakamura et al., 2003). In a study by Tamura et al. (2008), a decrease in melatonin levels and an increase in metabolic activity in the reproductive organs were observed when the pregnant woman was kept in constant light for 138 days (during 146 days of pregnancy). Furthermore, pinealectomy with melatonin therapy in pregnant women altered the daily pattern of fetal respiratory movements. This suggests that photoperiodic information provides circadian variations to the fetus through the mother's melatonin (Tamura et al., 2008).

IV. The Relationship Between Melatonin and Estrogen Hormone

Studies on melatonin have reported that it regulates the transcriptional activities of various nuclear receptors. It suppresses transcriptional activity on the glucocorticoid receptor (GR) and estrogen receptor alpha (ERα), while increasing Vitamin D receptor (VDR) and retinoic acid receptor alpha (RARα) activation (Hill et al., 2011; Hill et al., 2015).In a study by Soni et al. (2019), it was reported that follicle size growing with high levels of intrafollicular melatonin and low levels of MTRNA1 may also show activity in ovulation and folliculogenesis. The increase in estrogen receptor beta (ERβ) expression is associated with an increase in 17β-estradiol concentration and an increase in follicle size during the winter months. In another study conducted by Nakamura et al. (2003), "Intrafollicular melatonin and 17β-estradiol levels were shown to be lower in summer than in winter, and based on these findings, they stated that melatonin could play an important role in high-quality oocyte production thanks to its strong antioxidant activity (Nakamura et al., 2003).

V. The Function of Melatonin on the Ovary

Melatonin receptors have been demonstrated in various cell types in the uterus of the female reproductive tract. Many female reproductive hormones are regulated by endogenous circadian control, following 24-hour rhythms under both sleep-wake cycles and constant routine conditions (Rahman et al., 2019). Gamble et al. (2013) showed in their study that while these rhythms were preserved in the early follicular phase, they were significantly weakened in the luteal phase, where high progesterone secretions were dominant. It has also been shown that disruptions in the circadian system (e.g., shift work) adversely affect reproductive cycles (Gamble et al., 2013).

The presence of high melatonin concentration in follicular fluid (FF) compared to plasma circulation levels and the expression of MT1 and MT2 receptors in granulosa cells, luteal cells, antral follicles and corpus luteum of rats indicate that melatonin has many basic roles in the regulation of mammalian reproductive processes (Rönnberg et al., 1990). Detailed literature studies provide evidence that melatonin leads to alterations in steroidogenesis and follicular function in granulosa cells in birds, rodents, and humans (Tamura et al., 1998).

VI. Effect of Melatonin on Ovulation

Ovulation is a complex process in which a fertilizable oocyte is released into the oviductal lumen by rupturing the preovulatory follicle. This event occurs as a result of the timing-dependent dynamic interaction of local factors such as steroids, nitric oxide (NO), prostaglandins and peptides with LH fluctuation (Rai and Gosh, 2021). LH fluctuation activates the basic structural and biochemical changes that cause the rupture of Graafian follicles. This process triggers the release of a fertilizable oocyte followed by the formation of a corpus luteum (CL). In a study by Voordouw et al. (1998), it was reported that treatments with the combination of melatonin and progesterone (P) led to a decrease in LH secretion and consequently to the prevention of ovulation. In addition, such combination therapy has been reported to cause an increase in circulating P levels without any effect on FSH or inhibiting LH secretion (Voordouw et al., 1998). The effect of melatonin on hypothalamic gonadotropin release is also emphasized, possibly through the activation of the HPG axis (Roy and Granvord, 1987). The research of Tamura et al. (1998) reveals that large follicles show higher melatonin concentration compared to small follicles and therefore strongly suggests a positive correlation between follicular progesterone (P) and melatonin concentrations. It is thought that there is a relationship between prostaglandin E2 and melatonin. It is argued that melatonin has an inhibitory effect on prostaglandin E2 in the medial basal hypothalamus and is therefore indirectly important during signal transmission (Bettahi et al., 1998). In another study, melatonin was observed to suppress ovarian estrogen secretion in some mammals (so-called long-day reproducers). In contrast, in short-day breeding species such as sheep, reproductive control has been reported to be achieved by increasing estrogen synthesis of melatonin in the winter months (Yellon and Foster, 1986). Melatonin's interaction with estrodiol may also be regulatory during the cell cycle. Tamoxifen, a drug used for the interaction of melatonin with estrodiol, acts as an anti-estrogen steroid by stimulating estrodiol cell proliferation, initiating the progression of cell transcription stopped in the G1-S phase, while inhibiting cell proliferation in processes such as cancer. Thus, by stopping cell growth in the G1 phase of the cell cycle, it delays the transition to the S phase and thus slows down the cancer process (Cos et al., 2006). In their study, Cos et al. (1996) showed that melatonin hormone can delay the duration of the cell cycle by up to 15% for more than three hours and cell progression may stop in this process. Or, they reported that the participation of some stagnant and non-proliferating cells in the cycle may be delayed (Cos et al., 1996). Changes in the cell cycle often involve differences in the expression of some regulatory proteins. The regulatory effect of melatonin on the cell cycle is particularly associated with its effects on proteins involved in the G1-S transition. Research shows that melatonin can increase the expression of p53 and p21WAF1 proteins at the nanomolar level, indicating the potential to slow the progression of the cell cycle and support cellular repair processes (Mediavilla et al., 1999). P53is also known to be induced by melatonin. P53 also increases the expression of the p21WAF1 gene by regulating the cell cycle. Thus, it leads to inhibition of cyclin-dependent kinases and inhibition of phosphorylation of retinoblastoma protein, thereby stopping the transition of cells from G1 to S phase. The fact that melatonin increases the expression of p53 and p21WAF1 proteins is considered an important mechanism that causes the delay of the transition at the G1-S interface of the cell cycle (Malamud and Baserga, 1971; Cos et al., 2006).

VII. Result

In recent years, melatonin has attracted great attention with its capacity to scavenge free radicals. This has taken an important step towards a better understanding of the pleyotropic (multifaceted) physiological effects of melatonin. Some of these effects are receptor-dependent, while others occur independently of the receptor. Melatonin secreted from the pineal gland has also been reported to be present in follicular fluid (FF) after

circulation. It is known that the production of free radicals increases during the ovulation process. Melatonin, thanks to its powerful antioxidant and free radical scavenging properties, neutralizes these radicals, reduces oxidative stress and thus plays an important role in ovulation, oocyte maturation and embryo development. In addition, research into the potential roles of melatonin in human reproductive physiology shows that, despite the passage of time, our scientific knowledge is still insufficient in this regard. First, melatonin can reach almost any cell in the body; it can transmit circadian information through melatonin rhythms in plasma; and it can also act as a paracrine modulator of processes such as local oxidative state, inflammatory responses, and autophagy in organs such as the ovary and placenta. In some different physiological situations, melatonin acts as a permissive or synergistic signal and may affect the response of tissues to other molecules (e.g., oxytocin in the uterus). It is also clear that it has a role on the female reproductive system thanks to the melatonin hormone and the receptors it binds to. As an ancient molecule that is a member of various cellular processes, the involvement of melatonin in human reproduction can best be described as subtle, varied, and fundamental. For example, melatonin seems to contribute by keeping the heart of the circadian rhythm in all these processes, from fetal programming in the uterus to the timing of birth, from the effects on metabolism in important reproductive tissues to the regulation of neuroendocrine rhythms.

Binding of melatonin to specific membrane receptors (MT-1) can also trigger the interactions of hormones such as estrogen and progesterone, acting as a selective estrogen receptor modulator; or it can also replace a selective estrogen enzyme modulator, reducing the activity of aromatase and mRNA steady-state levels, the enzyme responsible for the local synthesis of estrogens. This shows that melatonin and estrogen can be considered together in terms of the female reproductive system.

As a result, embryological developmental stages, gender differences, and genetic variations can all affect how reproductive tissue reacts to melatonin. Melatonin can act as an important receptor in this pathway. Clearly, new analogues of melatonin and/or melatonin will eventually find their place in the arsenal of reproductive medicine in ways we probably can't even imagine.

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