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REVIEW

New developments of the effect of melatonin on reproduction

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Abstract

In the past decades, a lot of advances in understanding the biochemistry and physiology of the pineal gland have been made. There is evidence that it interacts with many endocrine as well as non-endocrine tissues to influence their metabolic activity modulating many organs and functions. Melatonin is secreted by the pineal gland in the brain and plays an important role in regulating the neuroendocrine system. This hormone is one of the major role players in the regulation of the circadian sleep-wake cycle. It is normally released from the pineal gland during the night in response to environmental changes in light. Studies have shown that melatonin plays a role in the regulation of many reproductive processes such as puberty, gonadal function, and pregnancy. Beside these, melatonin has been shown to be able to directly neutralize a number of free radicals and reactive oxygen and nitrogen species. The main objective of this review is to provide comprehensive information about the new developments in melatonin research regarding its role in reproduction. A review of international scientific literature was done and a question-and-answer format was used in an attempt to convey comprehensive information in a simple manner. This review discusses evidence currently available relating to the effect of melatonin on reproductive processes. It deliberates the mechanism of action of melatonin, its effect on puberty, testicular and ova function, pregnancy, and oxidative stress. A growing body of scientific evidence is suggesting that melatonin plays an important role in reproductive function. It is therefore imperative to highlight the beneficial effects of this hormone in improving the reproductive processes.

Key words: Melatonin; Reproduction; Reactive oxygen species; Antioxidants; Pineal gland

Core tip: In recent years, many studies have been focusing on the role melatonin plays in the process of reproduction. The low success rate in assisted reproductive technologies due to the detrimental effects of oxidative stress has led to studies investigating the potency of melatonin as an antioxidant. Studies have shown that melatonin reduces oxidative stress and contributes to oocyte maturation, embryo development, and luteinization of granulosa cells. Clinical studies have demonstrated that melatonin treatment for infertile women increases intra-follicular melatonin concentrations, reduces intra-follicular oxidative damage, and increases the chances of pregnancy. This review highlights the effects of melatonin in reproduction.

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INTRODUCTION

In the past few decades, a lot of studies regarding the biochemistry and physiology of a hormone called melatonin (*N*-acetyl-5-methoxytryptamine) have taken place. This hormone is secreted during the dark hours at night by the pineal gland and is responsible for the regulation of a variety of important central and peripheral actions

related to circadian rhythms and reproduction[1]. Although melatonin is primarily synthesized and secreted by the pineal gland, it is has been reported that it is also formed in tiny amounts by other organs such as the retina, harderian gland, gastrointestinal tract, lymphocytes, and the skin[2-5]. The role of melatonin in other animal species is related to seasonal reproductive cycles. In humans, melatonin secretion levels by the pineal gland can regulate the reproductive neuroendocrine axis[6]. The increase in reactive oxygen species (ROS) generation in *in vitro* fertilization (IVF) settings has been reported to negatively affect the success rate of IVF outcomes[7-9].

Melatonin has also been reported to have free radical scavenging properties[10,11] as well as stimulating several other antioxidant enzymes[12]. Can melatonin supplementation during assisted reproductive technologies increase the success rate of these procedures? Since the body is capable of producing melatonin does endogenous melatonin production or exogenous melatonin supplementation has any effect on the reproductive processes of humans and animals?

This review will provide comprehensive information about the new developments in melatonin research specifically regarding its role in the process of reproduction of both humans and animals. It will discuss the mechanism of action of melatonin, its effect on puberty, testicular and ovarian function, pregnancy, and oxidative stress.

CURRENT AVAILABLE EVIDENCE CONCERNING THE EFFECT OF MELATONIN ON THE REPRODUCTIVE PROCESS

What is the effect of melatonin on seasonal reproduction?

There is accumulation of evidence suggesting that the pattern of melatonin secretion, which is mediated by photoperiod, directly influences reproductive function. Much of the evidence has been generated from seasonally breeding mammals[13-16]. Long-day breeding animals such as rodents have been shown to be depressed during winter months (when elevated melatonin levels are at their longest nocturnal duration). The reproductive quiescent period was also prevented by surgical removal of the pineal gland[17]. On the other hand, short-day breeders such as sheep, and white-tailed deer were shown to be sexually very active and capable during the shortest days of the year, when melatonin levels are highest in terms of their nocturnal duration[18,19]. These observations suggest that melatonin is neither antigonadotrophic nor progonadotrophic. Thus, the changing duration of the nocturnal melatonin message is a passive signal that provides the hypothalamo-pituitary-gonadal (HPG)-axis information as to the time of year[20].

In a study involving male and female Syrian hamsters which were maintained under naturally occurring short days and reduced temperatures, it was observed that they developed gonadal regression. This regression was reversed by surgical removal of the pineal gland[21]. This is evidence that the reproductive axis obviously uses the seasonally dependent melatonin rhythm to adjust testicular and ovarian physiology accordingly.

Investigations using long-day and short-day breeding animals have enormously contributed to the understanding of the mechanisms whereby day length and melatonin govern seasonal reproduction. These findings have led to the successful use of melatonin as a pharmacological agent to advance the breeding season of sheep and to induce estrous cycles and increase lambing during the interval when these animals would normally be experiencing seasonal anestrus[22-24].

How does melatonin influence the selection of sexual mates?

Some studies have demonstrated that melatonin may be involved in the selection of sexual partner. It was observed that administering melatonin to male zebra finches in the drinking fluid in combination with carotenoids enhanced the brightness of the carotenoid-based pigmentation in their bills[25]. Since males with brighter coloured bills are more likely to be selected as a mate by females, melatonin may aid in the selection of a mate. Colourful plumage generally signals superior genetic quality and is common ploy used by many bird species as a sexual attractant[26].

More evidence of the role of melatonin on the selection of sexual mate has been demonstrated by the two-spotted goby fish[27]. Treating the skin explants of gobies with a combination of either melatonin and melanocyte-stimulating hormone or melatonin and prolactin, led to an exaggerated orange colouration and transparency of the belly skin. This colouration change induced by melatonin and other hormones would presumably benefit the individual in terms of attracting a sexual mate.

PINEAL MELATONIN BIOSYNTHESIS AND REGULATION

How is melatonin synthesized and regulated?

The production of melatonin by the pineal gland exhibits a circadian rhythm with low level of production during day time and high levels during the night[28,29]. During the process of melatonin synthesis, Tryptophan is hydroxylated to 5-hydroxy-tryptophan and subsequently into serotonin. Serotonin is acetylated to form *N*-acetylserotonin and then converted into melatonin (Figure 1). The suprachiasmatic nucleus (SCN) which is the major circadian oscillator that receives light input from the retina through the retino-hypothalamic tract is the one that regulate the circadian melatonin production[30]. When melatonin is formed in the pineal gland, it is not stored there, but released immediately into the blood or into the cerebrospinal fluid. It is metabolized mainly in the liver.

What is the mechanism of action of melatonin?

Melatonin exerts its actions through two types of recep-

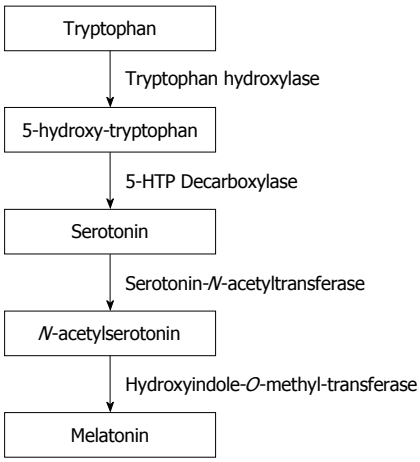

Figure 1 Biosynthesis of melatonin. 5-HTP: 5-hydroxy-tryptophan.

tors belonging to the super-family of G-protein coupled receptors. These receptors contain seven typical transmembrane domains and are called the MT_1 and MT_2[31,32]. The MT_1 and MT_2 are membrane bound receptors which are widely distributed in different organs of the body, including the brain and other peripheral organs.

When these receptors are activated they cause inhibition of adenyl cyclase activity[33] and inhibition of forskolin-induced cyclic adenosine monophosphate (cAMP) formation which result in the reduction in activated protein kinase[34]. In mammals melatonin has been reported to affect the reproductive function by activation of melatonin receptor sites within the HPG-axis[35].

Neonatal pituitary cells have been shown to express MT_1 and MT_2 subtype of melatonin receptors. These receptors when activated lead to a decrease in cAMP production and activity of protein kinase A, and attenuation of gonadotropic releasing hormone (GnRH)-induced gonadotropin secretion[36].

EFFECT OF MELATONIN ON PUBERTY

What is the effect of melatonin on the onset of puberty?

During fetal life and the first year of life, the HPG-axis is active, but becomes quiescent thereafter until around 10 years. Its reactivation depends on the progressive increase in the levels of GnRH which subsequently lead to the pulsatile secretion of luteinizing hormone (LH) and follicle stimulating hormone[37]. It has been reported that melatonin secretion has an inhibitory influence on the hypothalamic secretion of GnRH in humans[38]. It is therefore speculated that before puberty, melatonin concentrations are too high thus inhibiting the hypothalamic activation. But prior to puberty, the levels of melatonin decline below the threshold value thus forming the trigger signals of GnRH from the hypothalamus which leads to the onset of pubertal changes[39]. Therefore, it is the decline of melatonin levels that trigger puberty. Studies have demonstrated that high nocturnal melatonin secretion in children delays puberty[40] whereas low levels of melatonin have been shown to be associated with precocious puberty[41].

How does melatonin modulate sexual maturation?

The mechanism by which the HPG-axis is inhibited by melatonin after the first year of life until puberty is not well elucidated. However, there are reports that point to the influence of melatonin on the HPG-axis. These include, the evidence that melatonin is involved in the control of pulsatile secretion of LH[42] and that there is a negative correlation between nocturnal melatonin and LH concentrations[43]. Furthermore, high levels of serum melatonin in women have been shown to be associated with amenorrhea accompanied with decreased GnRH/LH pulsatile secretion[44,45]. Similarly, increases in nocturnal peak amplitude and duration of melatonin were reported in amenorrhoeic athletes who displayed irregularities in hypothalamic-pituitary-ovarian-axis functioning[46,47]. *In vitro* studies have demonstrated that melatonin leads to the down-regulation of the *GnRH* gene expression in a cell line containing GnRH secreting neurons[48].

MELATONIN AND GAMETE FUNCTION

What is the effect of melatonin on testicular function?

In animal studies, it has been shown that melatonin may modulate testicular function. In mice and rats it was reported that melatonin has an inhibitory effect on Leydig cells[49,50]. The Leydig cells are responsible for the production of testosterone. Mel_{1a} and Mel_{1b} receptor mRNAs are expressed in epithelial cells of rat epididymis suggesting that melatonin has a role in the regulation of epididymal physiology[51]. The epididymis is important for the maturation and storage of spermatozoa before they are ejaculated into the female reproductive tract.

There are contradictory reports concerning the effect of melatonin on spermatozoa function. It has been reported that long term administration of melatonin to healthy men is associated with decreased semen quality[52]. Sperm concentration, motility as well as testosterone levels were found to be significantly decreased in healthy men administered with melatonin. On the other hand, an *in vitro* study demonstrated that administration of melatonin to human spermatozoa improved progressive motility and reduced the number of static cells[53]. In another study in which melatonin levels were measured in fertile and infertile men, it was found that serum and seminal melatonin levels in infertile men were significantly reduced compared with the levels in the fertile men[54]. This demonstrated that melatonin may be involved in the modulation of the reproductive neuroendocrine axis in male infertility.

What is the effect of melatonin on ovary function?

The role of melatonin in the production of female gametes is focused on its direct actions in the ovary. It is able to pass through all cell membranes and enter all tissues because of its lipophilic property, however, it specifically concentrates in the ovary when injected systemically[55]. Studies have shown that high levels of melatonin are found in human preovulatory follicular fluid at concen-

trations which are much higher than those in serum[56,57]. It has been reported that the follicular fluid melatonin levels depend on the follicular growth[58]. The larger the follicle the higher the melatonin concentration. When oocytes are incubated in medium with melatonin supplementation during *in vitro* maturation, they have lower levels of ROS than control (without melatonin treatment) oocytes[59]. The ability of melatonin to promote embryo development in different species has correspondingly been reported. When mouse embryos were cultured in medium containing melatonin, increased blastocyst development rates were observed[60]. This suggests that melatonin may be involved in embryo development.

EFFECT OF MELATONIN ON PREGNANCY

What role does melatonin play in human pregnancy?

People living in the Arctic region have shown that their pituitary-gonadal function and conception rates are lower in the dark winter months than in the summer[61]. It has been further observed that during these dark periods of the winter season, the increases in serum melatonin concentration correlate with reduced activity of the anterior pituitary-ovarian axis[62]. The precise role of melatonin in human pregnancy is not clear. However, it has been reported that serum melatonin levels are higher during pregnancy than in nonpregnant women[63]. Moreover, twin pregnancies have been reported to yield higher nocturnal melatonin levels than singleton pregnancies[63]. This suggests that melatonin might have a role to play in human pregnancy. Clinical studies have demonstrated that melatonin treatment for infertile women increases intra-follicular melatonin concentrations, reduces intra-follicular oxidative damage and elevates fertilization and pregnancy rates[8].

Does melatonin play a role in fetal development?

Because melatonin is a small molecule, it gets transferred from the maternal circulation into that of the fetus through the placenta[64]. This means that the fetal circulation mirrors a circadian rhythm of plasma melatonin similar to that of the mother[65]. It has also been reported that there are melatonin receptors in the human fetal SCN. It is believed that melatonin is involved in the regulation of the circadian rhythm in the fetus. It has been observed that if maternal melatonin is suppressed, both *MT1* gene and clock genes are affected, suggesting that maternal melatonin has a role in modulating fetal clock gene function[66]. The generation as well as maintenance of circadian clock function depends on clock genes[67].

What is the role of melatonin in parturition?

In some mammals such as rats, parturition occurs during daytime[68]. Continuous darkness abolishes the photoperiodic timing of parturition[69]. If the pineal gland is removed in rats, the daytime delivery birth pattern is abolished and melatonin replacement therapy restores it[70]. It is well documented that the human myometrium has functional melatonin receptors[71]. Administration of melatonin has been shown to modulate the strength of affinity of gap junctions found in the myometrium[72,73]. These gap junctions serve to coordinate individual myometrial cell contractions into powerful labor inducing forces[72], thus implicating melatonin as a possible role player in the mechanism underlying the initiation of parturition.

MELATONIN AND OXIDATIVE STRESS

What are the sources of oxidative stress in the human reproductive system?

In females ROS is locally produced during the rupturing of the follicle at the time of ovulation[74]. It has been suggested that the ROS are involved in the ovulation process. There is a surge of LH during ovulation which induces dissolution of the basement membrane between the granulosa and theca internal layers and an expansion of the theca capillaries into the avascular granulosa cell layer to form a dense network of capillaries. These endothelial cell capillaries contribute to the generation of the free radicals[74]. Neutrophils and macrophages are also reported to reside in follicles[75]. These macrophages and neutrophils produce tremendous amounts of free radicals. The locally produced free radicals seems to have an important role on follicle rupture, since ROS have been shown to act as second messengers modulating the expression of genes that govern physiological processes of oocyte maturation[76,77]. However, excess ROS is responsible for oxidative stress which can damage molecules and structures of oocyte and granulosa cells within the follicle. Hence the ROS must be continuously scavenged to keep only small amounts necessary to maintain normal cell function.

In the male reproductive system, the cellular component of semen is a huge source of ROS. Morphologically abnormal and immature spermatozoa together with the presence of leukocytes can generate ROS in human ejaculates. Spermatozoa do generate ROS at the level of the plasma membrane and mitochondria[78]. Studies have shown that human spermatozoa generate superoxide (O_2^-), which spontaneously dismutates to hydrogen peroxide (H_2O_2)[79].

In the male genital tract and the ejaculate, ROS are not only derived from the spermatozoa, but can also be generated by leukocytes, which physiologically produce even up to 1000 times more ROS than spermatozoa[80,81]. This high ROS production by leukocytes plays a major role in infections, inflammation and cellular defense mechanisms. Basically, the cellular mechanisms for the generation of ROS in leukocytes and spermatozoa are the same, yet in leukocytes it is a physiological necessity to release large amounts of O_2^- into phagocytic vesicles during the killing action of pathogens.

Considering the extraordinary high content of polyunsaturated fatty acids in their membrane, the sperm plasma membrane is particularly susceptible to oxidative stress and the double bonds of the membrane lipids can

easily be oxidized by excessive ROS levels present in the sperm cells' environment. These can either be produced in large amounts by leukocytes or the spermatozoa themselves. In case of ROS attacking the plasma membrane lipids, a process called "lipid peroxidation" is initiated. Ultimately, this process decreases membrane fluidity of both plasma and organelle membranes and, as a result, damages membrane function, ion gradients, receptor-mediated signal transduction, *etc*[82]. Hence, with the loss of membrane function, spermatozoa lose the ability to function properly and therefore, fertilization is impaired[83].

Is melatonin a free radical scavenger?

Usually melatonin exerts its effects through its receptors, but it can also act directly as a powerful free radical scavenger by detoxifying the highly reactive hydroxyl radical[84,85]. There are numerous other reports confirming the scavenging abilities of melatonin on ROS and reactive nitrogen species[86,87]. Some of the free radicals scavenged by melatonin include O_2^-, H_2O_2, hydrochlorous acid, nitric oxide and the peroxynitrite anion[88-91]. The antioxidant properties of melatonin as a cell protector have been extensively studied and its scavenging ability have been reported to be higher than that of well known scavengers such as vitamin C and vitamin E[86]. Apart from scavenging free radicals directly, melatonin has a high capability to detoxify ROS and suppress its oxidative effects indirectly by enhancing the production of endogenous antioxidants. Melatonin has been shown to stimulate the scavenging activities and mRNA levels of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and catalase[92,93].

CONCLUSION

In recent years, a lot of research focused on the effect of melatonin as a direct free radical scavenger. This has greatly broadened our understanding of its multiple physiological roles. Melatonin's role in the regulation of reproductive physiology has been demonstrated in photoperiod dependent breeding mammals, and it seems to be receptor mediated mechanism in hypothalamus and pituitary gland. Currently, most of the research on melatonin is focusing on its local role as an antioxidant. The intrafollicular role of melatonin in the ovary has been demonstrated. Melatonin, secreted by the pineal gland, has been reported to be taken up into the follicular fluid from the blood. The free radicals produced within the follicles, especially during the ovulation process, are scavenged by melatonin, and reduced oxidative stress may be involved in oocyte maturation and embryo development. Evidence is pointing to the fact that melatonin treatment for infertility in women increases intra-follicular melatonin concentrations which subsequently reduces intra-follicular oxidative damage and elevates fertilization and pregnancy rates. The safety of exogenous melatonin treatment has been demonstrated in many studies[94,95]. Animal studies have also shown that melatonin has no detrimental effects on mouse and rat embryo development both *in vitro* and *in vivo*[96,97]. Future studies will indicate whether melatonin treatment could become a new cure for improving oocyte and sperm quality in infertile patients.

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