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Review Article

Melatonin in male and female fertility

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ABSTRACT

Melatonin, a hormone synthesized mainly by the pineal gland, has been found in extra-pineal organs as well. It's known as an organizer of circadian rhythms and more recently as an anti-oxidant. In addition to its role in maintaining immunity, pathophysiology of cardiovascular and neurological diseases, and as an anti-cancer agent. Evidence has demonstrated that melatonin exerts a positive impact on male and female fertility primarily through oxygen scavenging effects. Melatonin might have positive effects on nuclear and cytoplasmic maturation of oocytes and it probably opposes meiotic errors in old age oocytes. In Assisted reproductive technologies, supplementation of melatonin was shown be associated with better outcomes in terms of sperm quality, oocyte quality, embryo quality and pregnancy rates. Melatonin possibly shows promise as a supportive treatment in cases of infertility, thus trying to reach more understanding about its role in fertility is mandatory. Previous research has shown contradicting results regarding the role of melatonin in fertility. This review summarizes various actions of melatonin on the body focusing on male and female fecundity.

Introduction

Melatonin is formed and released primarily by the pineal gland (1). Furthermore, it can be produced by other organs as it has been found in extra-pineal organs, including digestive system, brain, eye, respiratory system, skin, renal system, thyroid, thymus, immune system and reproductive system (2- 12).

The discovery of melatonin by Lerner and team in 1958 has led to a new research area in the physiology of reproduction (1). Melatonin might have an essential role in regulating men and women fertility (2).

Recently, it has been shown that oxidative stress, an imbalance between reactive oxygen and nitrogen species, and antioxidants, is a contributing factor for decreasing fertility in both genders (13, 14).

Evidence showed that oxidative stress might negatively influence the success of In vitro fertilization (IVF) programs (15), therefore, melatonin, as one of the novel oxygen scavengers, has been used to decrease oxidative stress and to enhance IVF outcome. Its antioxidant effects as a strong radical scavenger may enhance oocyte quality directly since it is a potent antioxidant present in the follicular fluid (2, 16, 17).

Melatonin probably acts as a supportive therapy in patients with infertility, thus trying to reach greater understanding about its mechanism of action in fecundity is essential.

This review aims to briefly discuss the impacts of melatonin on body systems shedding the light mainly on its role in male and female fertility.

Synthesis of Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an Indoleamine that is produced from an essential amino acid called tryptophan. Its synthesis depends on the presence and absence of light as it is suppressed at daylight and stimulated at night (2). Thus, the release of melatonin displays a diurnal rhythm, started to be secreted in the evening, showing the highest level in the middle of the night (18).

Effects of melatonin on the body:

Melatonin has diverse range of effects on the body including its effects on the following systems:

Melatonin affects the immune system as Carrillo-Vico et al, suggested that melatonin can act as an immune buffer that boosts the immune system in basal and immunosuppressive states and suppresses the inflammation in conditions of exacerbation of immune reactions (19). The two types of melatonin receptors; the membrane and the nuclear receptors have been recognized on white blood cells. Membrane receptors were mainly present on CD4 T lymphocytes, CD8 T and B cells (20, 21). Melatonin regulates the production of cytokines by mononuclear cells (22). It has been stated that melatonin activates the innate immunity and the adaptive immunity. In contrast, melatonin can reduce the inflammation via the prevention of nuclear factor Kappa B binding to DNA and the inhibition of its translocation to the nucleus, these effects decrease cytokines and chemokines production (23).

Melatonin has been reported to be an anti-cancer agent as it acts against proliferation and metastasis, and it has pro-apoptotic and immunostimulatory properties (24), it has been suggested that it can be used in the treatment of some malignancies (24- 26). Melatonin may exert its anti- cancer action when it's used solely or combined with other anti- cancer therapies (27).

Evidence has proposed that melatonin has an essential role in the pathophysiology of some cardiovascular diseases (28, 29). A recent study has stated that melatonin can protect against myocardial damage resulted from high fat diet (30).

It has been shown that melatonin can maintain the integrity of blood brain barrier (31). Besides its ability of crossing the blood brain barrier, its capability to reduce oxidative stress and inflammation and its action as an anti- excitotoxicity and anti- misfolding make it a promising neuroprotector in some neurological diseases (32).

Melatonin and male fertility:

The hypothalamic pituitary testicular axis acts through positive and negative feedbacks, to regulate the function of the testis. The hypothalamus releases Gonadotropin releasing hormone (GnRH) in a pulsatile manner triggering the secretion of gonadotropins namely Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) from the anterior pituitary gland, those hormones mediate testicular functions, steroidogenesis and spermatogenesis (33).

Melatonin has a role in regulating the release of GnRH and LH (34). In a study done on sheep, it has been shown that melatonin suppresses LH release (35). Another study done on neonatal rats showed that inhibiting LH secretion by melatonin could be explained by a decrease of both second messengers (Ca2+) and cyclic AMP (36).

However, no impact of melatonin was found on LH, FSH and testosterone levels when administered for long term to normal males (37). Thus, more research is mandatory to illustrate melatonin's influence on hypothalamic pituitary testicular axis.

Melatonin is considered as a regulator of testicular steroidogenesis (34). In mice that received melatonin treatment, there were reductions in nuclear volume, endoplasmic reticulum volume, mitochondria and Golgi complex volumes of mice Leydig cells suggesting that such effects can probably inhibit Leydig cells from secreting testosterone (38).

Melatonin administration can also decrease Leydig cell cyclic AMP concentrations which is important in testosterone synthesis via LH signaling and this effect can be abolished by giving luzindole which is a melatonin receptor antagonist that stimulates testicular steroidogenesis, melatonin also suppresses Leydig cell steroidogenesis through inhibiting the expression of Steroidogenic Acute Regulatory Protein in MA- 10 mice (39).

Spermatozoa are considered highly susceptible for oxidative stress (40). A recent study done on rabbit's spermatozoa revealed that melatonin protects spermatozoa from reactive oxygen species (ROS) by improving AMP activated protein kinase (AMPK) phosphorylation (41).

Regarding human spermatozoa, Deng et al, showed that addition of melatonin to the cryoprotectant during the process of semen cryopreservation improves spermatozoa viability, and membrane integrity, and reduces intracellular ROS and lipid peroxidation damage. Furthermore, melatonin enhances heat shock protein (HSP90) expression in frozen–thawed sperms through melatonin receptor MT1 (42). Another study has reported that melatonin has free radical scavenging effects because it opposed sperm apoptosis in ejaculated human spermatozoa (43).

A recent study done on bull spermatozoa suggested that melatonin has capacitation-modulating effect and protective action at physiological concentrations (44).

Various studies have mentioned a decline of semen quality all over the world (45- 48). Semen quality is considered a marker for male fertility, thus trials to find factors improving it are essential.

Researchers evaluated melatonin effects on the quality of rooster sperms comparing it with control samples with no added melatonin, found that sperm count is greater in samples with melatonin, cell membrane performance and mitochondrial function are also better in melatonin samples than the control samples. In addition, oxidative degradation of lipids, DNA fragmentation, and apoptosis were all less in samples treated with melatonin (49).

In human, post- thaw sperms that have been treated with various melatonin concentrations (0.001, 0.005, 0.01, 0.05, 0.1, and 1 mM), during the process of cryopreservation, showed better spontaneous

movement and survival with less intracellular ROS levels and malondialdehyde (MDA) levels than the control group in all melatonin doses except for 0.001 mM. Melatonin concentration of 0.01 mM was the most effective one in protecting spermatozoa from oxidative stress (50).

On the other hand, it was shown that administration of melatonin can negatively affect the semen quality in healthy men, this could be due to aromatase inhibition (51). However, in this study long term administration of melatonin was used and the study was done on healthy men.

Sharbatoghli et al, have not found a relationship between seminal plasma melatonin and sperm parameters, nonetheless, they showed that DNA fragmentation and melatonin levels are positively associated in infertile men (52).

A study done on human semen samples showed that melatonin reduces ROS that are derived from the mitochondria and it rescues the decreased penetration ability of spermatozoa treated with 3-Nitrophthalic acid (3-NPA) thus melatonin might have the clinical potential to enhance sperm quality (53).

A recent research compared the seminal plasma and serum melatonin levels of men with idiopathic oligoasthenoteratozoospermia and normal, fertile males. It evaluated the effects of exposure to light at night on semen parameters, the study demonstrated a significantly lower serum and seminal plasma levels of melatonin in patients exposed to light at night in comparison to non-exposed cases. Therefore, darkness and sleep at night-time may potentiate the semen parameters of males with idiopathic oligoasthenoteratozoospermia (54).

So, adequate melatonin level is crucial for improving male fertility. Its benefit is possibly evident mainly in cases of idiopathic infertility, however, administration of melatonin for long duration is not advised and further studies are necessary in this research area to illustrate the mechanisms of melatonin impact on semen quality.

Melatonin and female fertility:

Oxidative stress exerts toxic effects on the oocytes maturation. Evidence showed that melatonin might protect oocytes from free radical damage (55).

The process of oxidative damage in mice oocytes may happen as soon as eight hours following being in the culture, and it coexists with the appearance of markers of apoptosis like phosphatidylserine externalization, then, after 16 hours, caspase activation takes place along with structural alterations of oocyte biological aging as shown by Lord et al (56). The researchers of the same study also concluded that melatonin supplementation can prevent oxidative stress hence delay the aging process of mice oocytes, so it might be useful in clinical practice (56).

A review stated that ROS are produced in the follicles mainly during ovulation, they can be scavenged by melatonin thus reducing oxidative stress and improving oocyte maturation as illustrated in figure 1 (57).

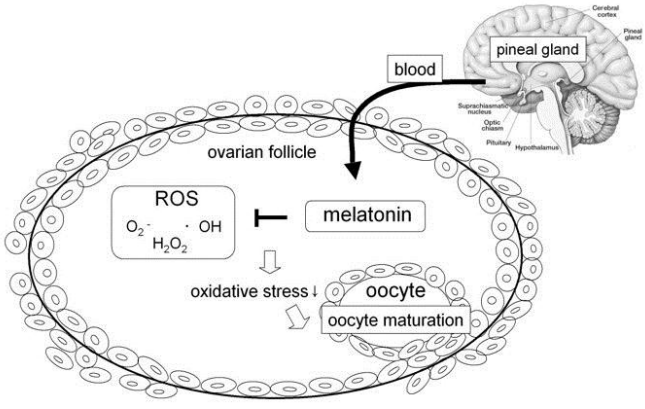

Figure 1. Role of melatonin as an antioxidant in ovarian antral follicle (57). This figure was published by BioMed Central Ltd/ part of Springer Nature (https://ovarianresearch.biomedcentral.com/articles/10.1186/1757-2215-5-5/figures/4), distributed under the terms of the Creative Commons Attribution License 2.0 (http://creativecommons.org/licenses/by/2.0) *the title of this figure is modified from the original reference.

In a study done by Kang et al, the researchers compared porcine oocytes treated with melatonin and those that are not treated, during the process of In vitro maturation (IVM). It was found that ROS are significantly lower in oocytes treated with melatonin. Also, melatonin has had positive effects on nuclear and cytoplasmic maturation of porcine oocytes (58). Another study has demonstrated that melatonin improves oocyte maturation and thus it possibly enhances oocyte quality and fertilization rates (55).

Evidence showed that melatonin administration potentiates oocyte maturation, embryo cleavage and blastocyst development rates in mice, nonetheless, the response to melatonin differs according to the doses used in various stages of maturation and development since cumulus oocyte complexes required lower melatonin concentration during maturation stages compared with oocytes without cumulus cells and embryos needed lower melatonin concentrations in this experiment (59).

Regarding human oocytes, Wei and coworkers, evaluated nuclear maturation of oocytes that were cultured in mediums treated with different melatonin concentrations, they found that low melatonin concentrations enhances nuclear maturation, whereas, high concentrations of melatonin decreases nuclear maturation (60). Further research is probably needed in this field to reach more understanding.

Yang et al, illustrated that melatonin can prevent oocyte aging following ovulation in mice as it decreased ROS and inhibited meiosis abnormalities, mitochondrial disorders, autophagocytosis and apoptosis via the upregulation of SIRT1 and MnSOD protein levels in postovulatory aged oocytes (61).

A more recent study, done in 2020, found that melatonin in the follicular fluid reduces with age in mice. Supplementation of old mice with melatonin can protect oocytes from spindle and chromosomal abnormalities and from aneuploidies. Melatonin

opposes meiotic errors in old age oocytes via stimulation of Sirt1/Sod2 pathway. The increment of Sirt1 expression in oocytes treated with melatonin promoted the expression of Sod2 thus reducing ROS and improving oocyte quality (62).

In women with Polycystic ovary syndrome (PCOS), it has been suggested that melatonin enhances the expression of cytochrome P450 family 19 subfamily A member 1 (CYP19A1) and heme oxygenase-1 (HO-1), and decreases the levels of interleukin 18 (IL-18) in the granulosa cells thus improving oocyte maturation in PCOS women with high androgen levels (63).

A research showed that women with unexplained infertility can also benefit from melatonin administration as two doses (three mg/day or six mg/day) of melatonin have been tried which probably led to decrement of oxidative stress and improvement of oocyte quality in patients with idiopathic infertility. Nonetheless, the authors of the study have encouraged more studies in people with various backgrounds to confirm the importance of melatonin in treating infertility (64).

Systematic review and meta-analysis of randomized controlled trials concluded that more research, regarding melatonin role in treating infertility, is needed before the application of the routine use of melatonin in practice (65).

Melatonin and In Vitro Fertilization (IVF):

In order to get high quantity of oocytes and to achieve good pregnancy rates, ovarian stimulation protocols are used in IVF (66). Nevertheless, they can increase oxidative stress since they might alter the follicular environment and affect the endogenous levels of oxygen scavengers (2, 66). Follicular fluid has strong anti-oxidant activity, however, the in vitro oocytes are not protected by this fluid thus they are highly susceptible to oxidative stress (2, 67). In addition, the high oxygen concentrations that oocytes may expose to in the incubators and throughout dealing with them in IVF procedures may increase ROS (2).

Reactive oxygen species generation in granulosa cells of females having IVF, mainly in cases of PCOS, might affect IVF success rates negatively (68). It has been suggested that the administration of micronutrients may exert positive effects on IVF results possibly by decreasing oxidative damage in serum and follicular fluid proteins thus improving oocyte quality (69).

A study demonstrated that treating women, who have unsuccessful IVF cycles previously, with melatonin can improve oocyte quality since the administration of melatonin tablet (three mg) can increase the concentration of intrafollicular melatonin and it can reduce the concentration of intrafollicular lipid peroxide (70). Rizzo et al, found that women with history of low oocyte quality who were given melatonin in addition to myo-inositol and folic acid in IVF cycles have had better oocyte quality, and pregnancy outcome than women who received myo-inositol and folic acid without melatonin (17).

In addition to the influence of melatonin on the sperms and the oocytes as mentioned previously, studies have found that it has beneficial effects on the embryos as well (71- 73). The environment that the embryos are cultured in is important to determine the success of fertilization and implantation (2). Rodriguez- Osorio and team found a positive impact of melatonin on porcine embryo cleavage rate and blastocyst cell numbers at a concentration of 10−9 m (71). In mice, it was found that melatonin potentiates the early growth of the embryos and the development rate to blastocysts, probably through its effect on the metabolism in early embryogenesis stages thus stimulating blastocysts formation (72). Also, melatonin was found to have beneficial influences on the embryos of the sheep through two mechanisms, by reducing the oxidative stress and by affecting the fertilization process positively (73).

Luteal phase insufficiency can result from free radical damage which might reduce the progesterone levels (74). Melatonin may support the luteal phase as a study showed that it potentiates progesterone production in human granulosa lutein cells (75). Another study, done on 66 women, showed that melatonin increases progesterone levels significantly in the treatment cycle in comparison to the preceding one, however, in the same study, it was noticed that melatonin enhances progesterone concentration non-significantly in the patients in comparison to the controls (76). Thus, more research is needed to investigate the effects of melatonin in supporting the luteal phase.

Studies have shown that melatonin might improve pregnancy rates (17, 55, 77). In a prospective trial involved 65 women, Rizzo et al, found that women with history of low oocyte quality who were given melatonin in addition to myo-inositol and folic acid in IVF cycles have had in tendency better clinical pregnancy rate compared with women who were not received melatonin, though the variation was not significant (17). So, using a combination of antioxidants during the treatment of infertility might improve the outcome. Tamura et al, have observed that the gestation rate was higher in patients received melatonin than patients with no melatonin (55). A randomized double blinded clinical trial was performed on PCOS patients underwent intrauterine insemination (IUI) treatment, compared two groups in term of chemical pregnancy rates; the group of women who were given melatonin, and the control group, the study showed that chemical pregnancy rates were 32% and 18% respectively with a p value of 0.012 (77).

Melatonin can be used as a supportive therapy in treating male infertility mainly in cases of unexplained infertility and in treating female infertility, especially in PCOS and unexplained infertility conditions. Studies showed contradicting results which could be due to heterogeneity of the patients involved in the studies, in terms of reasons of infertility, age groups and doses of melatonin used. Thus, more randomized controlled trials are essential to be done taking into consideration causes of these controversial findings.

Conclusion

Melatonin has been known as an anti-oxidant that exerts various effects on the body. It has also been used as an adjunctive treatment in cases of male and female infertility to reduce oxidative stress that can be associated with infertility, thus improving success rates of pregnancy mainly in IVF programs. However, its routine use in practice still needs further well-designed studies such as more randomized controlled trials in the field of fertility.

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Conflict of Interest
No conflict of interest

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