Melatonin in Infertility

Özlem Gün ERYILMAZ, Esma SARIKAYA

Ankara, Turkey

Melatonin, is the primary synchronizing agent acting primarily on the circadian sleep pattern and has some roles in reproduction. Melatonin receptors have been identified in suprachiasmatic nuclei, pars tuberalis, ovary, uterus, follicular cells, and the oocyte. Melatonin is also a direct free radical scavenger and modulates the oxidative environment in the reproductive tract. It serves as an anti-oxidant agent and protects the oocyte and the embryo from oxidative damage. In this review article, we summarized the likely fertility impairing activity of melatonin in the infertility treatments.

Key Words: Melatonin, Anti-oxidant, IVF

Gynecol Obstet Reprod Med 2011;17:191-194

Introduction

Melatonin, or N-acetyl-5-methoxytryptamine, produced mainly in the mammalian pineal gland, is the primary synchronizing agent of the circadian sleep pattern.[1] The relationship of the circadian rhythm and melatonin to the sleep-wake cycle has been extensively studied. Melatonin also has an important role in human reproduction.[2-4]

The effects of melatonin on reproduction are produced via the hypothalamus and the anterior pituitary.[5] Melatonin has multiple action sites in the reproductive system and other parts of the body. Its receptors have been demonstrated in the suprachiasmatic nuclei, pars tuberalis, ovaries and the uterus.[3,4,6]

The reproductive action of melatonin is produced by the direct binding of the hormone to its receptors and as a result of its antioxidant activity in the reproductive microenvironment, facilitating oocyte-sperm interaction, embryonic development, and implantation.

Reactive species and reproduction

Reactive oxygen species (ROS) are unstable molecules that are generated from aerobic metabolism. Their outer shells contain one or more unpaired electrons allowing them to interact with other molecules in order to achieve a stable configuration of electrons. Such reactions in turn convert other molecules into free radicals. Oxygen (O_2), with its two unpaired electrons, is highly prone to radical formation in biological systems. Molecules reacting with O_2 can produce free radicals, which have important effects on various organs.[7] Some of the most biologically-relevant free radicals are listed in table 1.

Table 1: Free radicals and toxic metabolites

Molecular oxygen	O_2
Superoxide radical	O_2-
Hydroxyl radical	$OH\bullet$
Alcoxyl radical	$RO\bullet$
Peroxyl radical	$ROO\bullet$
Hydrogen	$H\bullet$
Ozone	O_3
Hydrogen peroxide	H_2O_2

Antioxidant enzymes like superoxide dismutase (SOD), catalase and gluthatione peroxidase are involved in the neutralization of free radicals. Superoxide (O_2-) is produced by the transfer of an electron to an O_2 molecule, leaving a single unpaired electron. Further reduction of superoxide with a second electron results in the formation of hydrogen peroxide (H_2O_2). These free radicals can form other unstable molecules (Figure 1). Neutralization of O_2- and H_2O_2 by antioxidant molecules are shown in figure 2.

Figure 1: An example of a free radical reaction

$$O_2- + H_2O_2 \rightarrow OH\bullet + OH^- + O_2$$

Figure 2: The enzymatic pathway of the antioxidant action of catalase and superoxide dismutase. (SOD).

Toxic free radicals are converted to water and oxygen.

$$\text{SOD}: \quad O_2- \rightarrow H_2O_2 + O_2$$

SOD: Superoxide dismutase;

$$\text{GPx/Catalase}: \quad H_2O_2 \rightarrow H_2O$$

GPx: Gluthatione peroxidase/ Catalase

ROS cause cellular damage by interacting with intracellular components like lipids, proteins and nucleic acids.

Zekai Tahir Burak Women Education and Research Hospital, Department of Reproductive Endocrinology and Infertility, Ankara

Address of Correspondence: *Özlem Gün Eryılmaz*
Devlet Mah.Subay Loj.No:19/11
Bakanlıklar-Ankara
drozlemgun@yahoo.com

Submitted for Publication: *08. 09. 2011*
Accepted for Publication: *10. 10. 2011*

Exposure of cell membrane lipids to free radicals results in lipid peroxidation and disturbs membrane integrity, permeability and ion transport. Free radicals also act on the lysosomal membrane, resulting in increased permeability and release of various enzymes into the cytoplasm, triggering a cascade of intracellular destruction. Unlike nucleic acids whose interaction with free radicals may result in mutations and cell death, proteins are more resistant to the damaging effects of ROS.

Melatonin as a free radical scavenger

Free radicals co-exist with the protective family of antioxidant enzymes.[8] Some of the enzymatic and non-enzymatic antioxidants are presented in table 2. Non-enzymatic antioxidants are also known as free radical scavengers, which include alpha tocopherol (vitamin E), ascorbic acid (vitamin C) and uric acid. Melatonin, which possesses antioxidant activity, is another newly pronounced free radical scavenger.[9]

Table 2: Antioxidant mechanisms, enzymes and molecules

Mitochondrial cytochrome oxidase system
Superoxide dismutase
Catalase
Gluthatione peroxidase
α –tocopherol
β-carotene
Ascorbic acid
Urate
Cyctine
Ceruloplasmine
Transferin

Oxidative stress in infertility

The role of oxidative stress in female reproduction has been increasingly studied. Free radicals are regulatory mediators in ovarian functioning, including folliculogenesis and steroidogenesis.[10] Riley et al. demonstrated the action of ROS and antioxidant enzymes in oocyte maturation, ovulation, and luteal development.[11] Glutathione peroxidase and manganese superoxide dismutase (MnSOD), found to be expressed in metaphase II (MII) ooocytes, were two of the antioxidant enzymes involved in ovarian cycling activity.

The oxidative radicals play an important role as intracellular and intercellular messengers in the ovary and mediate a series of reactions involving ovarian germ cells and stromal cells.[13] ROS are neutralized by the ovarian antioxidant enzymes, which promote a protective microenvironment for the oocyte and the embryo.[14]

ROS and antioxidants are also expressed in the endometrium, where superoxide dismutase demonstrates a cyclic change. Decreased levels of the enzyme are seen in the late secretory phase.[15] Several studies were conducted to elucidate the role of oxidative species in menstruation and endometrial shedding. A correlation between ROS production and endometriosis was investigated. Some studies demonstrated increased levels of ROS in endometrial implants and peritoneal fluids of patients with endometriosis.[16,17] but others failed to confirm the role of ROS in the pathogenesis of endometriosis.[18,19]

Melatonin, a free radical scavenger[9]can inactivate oxygen and nitrogen radicals.[20,21] This action is exerted by melatonin and its metabolites (cyclic 3-hydroxmelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine, and N1-acetyl-5-methoxykynuramine).[22] All of the metabolites are present in ovarian tissue and follicular fluid.[23] The effects of melatonin on reproductive functioning were found to be a result of alteration of hormonal levels and by the antioxidant activity against oxidative stress.[24,25] Adriaens et al. demonstrated increased levels of progesterone and androgen in murine pre-antral follicles, cultured with melatonin.[26] Tanavde et al. also studied the effects of melatonin on follicular development and obtained similar results.[25] In pinealectomized animals, Soares et al. demonstrated an increased number of atretic follicles and hormonal imbalance with elevated estradiol and reduced progesterone levels.[27] These studies support the well known role of melatonin as a regulatory hormone of reproductive function and indicate that its disproportion may contribute to infertility.

Melatonin has an anti-ovulatory action when administered exogenously. It decreases luteinizing hormone levels and blocks ovulation, Luteal phase progesterone is increased by the effect of melatonin.[28]

In Vitro Fertilization (IVF) has also been studied in association with the application of melatonin. The main action of melatonin on the oocyte and the embryo may be via its antioxidant activity. Oxidative stress is associated with poor oocyte quality and fertilization failure.[29,30] Follicles and granulosa cells in such cases have been found to contain an increased level of ROS.[29] Hyrdroxyl radical, superoxide and hydrogen peroxide are the most commonly known free radicals and are believed to be responsible for the destruction of oocyte cell membranes, DNA damage and acceleration of apoptosis.[31] Fragmented embryos had higher levels of H_2O_2, when compared to those that were not fragmented, and levels of free radicals were higher in non-fertilized oocytes.[32] Increased levels of antioxidants were found in embryos with poor maturation, suggesting a reaction to increased oxidative stress.[33] Antioxidant enzymes have the key role of protecting the oocyte against these radicals. Paszkowski et al. studied gluthatione peroxidase and showed that the levels of the enzyme in the follicular fluid were lower in patients with unexplained infertility.[34]

Antioxidant administration for fertility treatments

In the light of these studies, it is thought that adequate antioxidant activity in the microenvironment of the reproductive organs may help to treat infertility. Therefore, exogenous administration of an antioxidant may increase fertility by improving the balance between ROS and antioxidants. Melatonin, a radical oxygen scavenger, can be used in the treatment of infertility.

Melatonin was used in women with a history of poor oocyte quality. Rizzo et al. used melatonin with myo-inositol (an amino acid involved in cell proliferation) and folic acid.[35] He studied the effects of melatonin in patients with a history of poor oocyte quality, and concluded that melatonin improved oocyte quality and increased the fertility rate when used together with myo-inositol and folic acid. The antioxidant action of melatonin was highlighted in their study. Tamura et al. also studied patients with poor oocyte quality in a previous IVF cycle and administered melatonin in the subsequent cycle.[36] Melatonin administration increased the rate of fertilization and pregnancy, and decreased the level of intrafollicular 8-hydroxy-2¢-deoxyguanosine (8-OHdG, a DNA repair enzyme whose concentration is a measurement of oxidative stress). Hemadi et al. administered melatonin to rats with transplanted ovaries and studied oocyte maturation.[37] He showed that in rats that were administered melatonin, primordial follicles of the grafted ovary developed into the next stage more efficiently and showed all of the necessary morphological changes of oocyte maturation. Eryilmaz et al. also showed the enhancing effect of melatonin on oocyte quality in patients who had sleep disturbances and were also receiving IVF treatment.[38]

Most of the studies showed the boosting impact of melatonin on fertility and IVF outcomes. Direct free radical scavenging, indirect antioxidant action and receptor modulated hormonal regulation are effects of melatonin described in association with reproduction. Melatonin activity in infertile women may be disturbed. Melatonin receptor defects may account for poor oocyte quality in unexplained infertility. Melatonin may take its place in the group of antioxidant drugs. More studies about melatonin and its effects on fertility may advance new treatment strategies or even help resolve infertility in a certain group of patients.

İnfertilite de Melatonin

Primer olarak uyku fizyolojisinde görev alan melatonin, aynı zamanda üreme fizyolojisinde de etkilidir. Melatonin reseptörleri, suprakiazmatik nükeusta, pars tuberaliste, overde, uterusta, folliküler hücrelerde ve oosit üzerinde tespit edilmiştir. Melatonin, direk serbest radikal koruyucusudur, bu etki ile oosit ve embiryoyu oksidatif zedelenmeden korur ve anti-oksidan etki ile mikro-ortamını iyileştirir. Derleme olarak sunduğumuz bu çalışmada, melatoninin, fertilite üzerindeki olumlu etkilerini ve infertilite tedavilerine olabilecek muhtemel faydalarını özetlemeye çalıştık.

Anahtar Kelimeler: Melatonin, Antioksidan, IVF

References

1. Dodson ER, Zee PC. Therapeutics for circadian rhythm sleep disorders. Sleep Med Clin 2010;5:701-15
2. Reiter RJ. Melatonin and human reproduction. Ann Med 1998;30:103-8
3. Yie SM, Niles LP, Younglai EV. Melatonin receptors on human granulose cell membranes. J Clin Endocrinol Metab 1995;80:1747-9
4. Woo MMM, Tai JC, Kank SK, Nathwani PM, Pang SF, et al. Direct action of melatonin in human granulose-luteal cells. J Clin Endocrinol Metab 2001;86:4789-97
5. Diaz Lopez B, Diaz Rodriguez E, Urquijo J, Fernandez Alvarez C. Melatonin imfluences on the neuruendocrine-reproductive axis. Ann N Y Acad Sci 2005;1057:337-64
6. Barrett P, Convay S, Morgan PJ. Digging-deep- structure-function relationship in the melatonin receptor family. J Pineal Res 2003;35:221-30
7. Reilly PM, Shiller HC, Burkley GB. Pharmacological Approach to tissue injury mediated by free radicals and other reactive oxygen metabolites. Am J Surg 1991; 161:488-503
8. Halliwel B, Gutteridge JW, Cross CE. Free radicals, antioxidants, and human disease:what are we know? J Lab Clin Med 1992; 119:598-620
9. Reiter RJ, Tan DX, Maldonado MD. Melatonin as an antioxidant: physiology versus pharmacology. J Pineal Res 2005;39:215-6
10. Behrman HR, Kodaman PH, Preston SL, et al. Oxidative stress and the ovary. J Soc Gynecol Invest 2001;8:S40-S42
11. Riley RC, Behrman HR. Oxygen radicals and reactive oxygen species in reproduction. Proc Soc Exp Biol Med 1991;198:781-91
12. El Mouatassim S, Guerin P, Menezo Y. Expression of genes encoding antioxidant enzymes in human and mouse oocytes during the final stages of maturation. Mol Hum Reprod 1999;5:720-25
13. Roselli M, Keller PJ, Dubey RK. Role of nitric oxide in the biology, physiology and pathophysiology of reproduction. Hum Reprod Update 1998;4:3-24
14. Sugino N, Takiguchi S, Ono M et al. Nitric oxide concentrations in the follicular fluid and apoptosis of granulose cells in human follicles. Hum Reprod 1996;11:2484-2487
15. Sugino N, Shimamura K, Takiguchi S et al. Changes in

activity of sureoxide dismutase in the human endometrium throughout the menstrual cycle and in early pregnancy. Hum Reprod 1996;11:1073-8

16. Murphy AA, Palinski W, Rankin S, Morales AJ, Parthasarathy S. Evidence for oxidatively modified lipid-protein complexes in endometrium and endometriosis. Fertil Steril 1998;69:1092-4
17. Osborn BH, Haney AF, Misukonis MA, Weinberg JB. Inducable nitric oxide synthase expression by peritoneal macrophages in endometriosis-associated infertility. Fertil Steril 2002;77:46-51
18. Bedaiwy MA, Falcone T, Sharma RK, Goldberg JM, Attaran M, Agarwal A. Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. Hum Reprod 2002;17:426-31
19. Wang Y, Sharma RK, Falcone T, Goldberg JM. Importance of reactive oxygen species in the peritoneal fluid of women with endometriosis and idiopathic infertility. Fertil Steril 1997;68:826-30
20. Tan DX, Reiter RJ, Manchester LC et al. Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger. Curr Top Med Chem 2002;2:181-97
21. Reiter RJ, Tan DX, Gitto E et al. Pharmacological utility of melatonin in reducing oxidative cellular and molecular damage. Pol J Pharmacol 2004;56:159-70
22. Tan DX, Manchester JC, Terron MP, Flores LJD, Reiter RJ. One molecule, many derivatives: a never ending interaction of melatonin with reactive oxygen and reactive nitrogen species? J Pineal Res 2007;42:28-42
23. Itoh MT, Ishizuka B, Kuribayashi Y, AmemiYa A, Sumi Y. Melatonin, its precursors and synthesizing enzyme activities in the human ovary. Mol Hum Reprod 1999;5:402-8
24. Adriaens J, Jacquet P, Cortvrindt R, Janssen K, Smitz J. Melatonin has dose-dependent effects on folliculogenesis, oocyte maturation capacity and steroidogenesis. Toxicology 2006;228:333-43
25. Tanavde VS, Maitra A. In vitro modulation of steroidogenesis and gene expression by melatonin:a study with porcine antral follicles. Endocrinol Res 2003;29:399-410
26. Adriaens J, Jacquet P, Cortvrindt R, Janssen K, Smitz J. Melatonin has dose-dependent effects on folliculogenesis , oocyte maturation capacity and steroidogenesis. Toxicology 2006;228:333-43
27. Soares JM, Simoes MJ, Oshima CT, Mora OA, De Lima GR, Baracat EC. Pinealectomy changes rat ovarian interstitial cell morphology and decreses progesterone receptor expression. Obstet Gynecol 2003;17:115-23
28. Voordouw BC, Euser R, Verdonk RE, et al. Melatonin and melatonin-progestin combinations alter pituitary ovarian functionin women and can inhibit ovulation. J Clin Endocrinol Metab 1992;74:108-17
29. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol 2005;3:28
30. Zuelke KA, Jones DP, Perreault SD. Gluthatione oxidation is associated with altered microtubule function and disrupted fertilization in mature hamster oocytes. Biol Reprod 1997;57:1413-9
31. Kowaltowski AJ, Vercesi AE. Mitochondrial damage induced by conditions of oxidative stress. Free Radic Biol Med 1999;26:463-71
32. Yang HW, Hwang KJ, Kwon HC, et al. Detection of reactive oxygen species (ROS) and apoptosis in human fragmented embryos. Hum Reprod 1998;13:998-1002
33. Paszkowski T, Clarke RN. Antioxidative capacity of preimplantation embryo culture medium declines following the incubation of poor quality embryos. Hum Reprod 1996;11:2493-5
34. Paszkowski T, Traub AI, Robinson SY, McMaster D. Selenium dependant gluthatione peroxidase activity in human follicular fluid. Clin Chim Acta 1995;236:173-80
35. Rizzo P, Raffone E, Benedetto V. Effect of the treatment with myo-inositol plus folic acid plus melatonin in comparison with a treatment with myo-inositol plus folic acid on oocyte quality and pregnancy outcome in IVF cycles. A prospective clinical trial. Eu Rev Med Pharmacol Sci 2010;14:555-61
36. Tamura H, Takasaki A, Miwa I, Taniguchi K, Maekawa R, Asada H. Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate. J. Pineal Res. 2008; 44:280-7
37. Hemadi M, Abolhassani F, Akbari M, et al. Melatonin promotes the cumulus-oocyte complexes quality of vitrified-thawed murine ovaries; with increased mean number of follicles survival and ovary size following heterotopic transplantation. Eu J Pharmacol 2009;618:84-90
38. Eryilmaz OG, Devran A, Sarikaya E, Aksakal FN, Mollamahmutoğlu L, Cicek N. Melatonin improves the oocyte and the embryo in IVF patients with sleep disturbances, but does not improve the sleeping problems. J Assist Reprod Genet. 2011 Jul 12. [Epub ahead of print])