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ERKEK İNFERTİLİTESİNDE STRESİN ROLÜ VE UYGULANAN GÜNCEL MELATONİN HORMON TEDAVİLERİNİN ETKİSİNİN İNCELENMESİ

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ÖZET. Psikolojik, fizyolojik, sosyal hatta çevresel kaynaklı nedenlerle canlıda ki homeostatik mekanizmalarda meydana gelen bozulmalar şeklinde tanımlanan stres kavramı üzerinde 17 yüzyıldan bu yana bahsedilmekle birlikte modern yaşamda sıklıkla karşımıza çıkmaktadır. Öyle ki ev, iş yaşamından tutun sokakta, trafikte yaşamın herhangi bir anında strese maruz kalınabilmektedir. Bu durum stresi modern yaşamın bir parçası haline getirmiştir. Yakın birini kaybı, işyeri stresi hatta COVID 19 pandemisinde bireylerin evlerde izole bir şekilde yaşamı gibi herhangi bir durum veya olay da stres kaynağı olabilmektedir. Strese uyaranına karşı canlıda meydana gelen yanıtlar belirli bir düzeye kadar canlının faydasına yöneliktir. Ancak stres uyaranın süresi ve şiddetinin artması durumlarında tüm fizyolojik sistemlerde patolojik durumlar şekillenmektedir. Uzun süreli stres maruziyeti, sperm kalitesi, sperm konsantrasyonu, spermatozoit sayısı, sperm yüzdesi gibi sperm parametrelerinde azalmalara neden olarak erkeklerde infertiliteye yol açabilmektedir. Stresin üreme sistemindeki bu olumsuz etkilerini azaltmak adına çeşitli maddeler araştırılmaktadır. Yapılan çalışmalarda melatoninin antioksidan, anti-inflamatuar, anti-apipotik vb. mekanizmalar ile erkek infertilitesinde olumlu etkinlik göstermektedir. Bu derlemede stresin erkek üreme sistemi üzerine etkisi ve melatonin ilişkisi üzerinde bilgi verilmesi amaçlanmaktadır.

Anahtar Kelimeler: Erkek infertilitesi, Melatonin, Sperm, Stres.

INVESTIGATION OF THE ROLE OF STRESS IN MALE INFERTILITY AND THE EFFECT OF CURRENT MELATONIN HORMONE TREATMENTS

ABSTRACT. Although stress, defined as the deterioration in homeostatic mechanisms in living things due to psychological, physiological, social, and even environmental reasons, has been mentioned since the 17th century, it is frequently encountered in modern life. So much so that you can be exposed to stress anytime, from home, business life, to the street, in traffic. This situation has made stress a part of modern life. Any situation or event, such as losing a close person, workplace stress, or even living in isolation at home during the coronavirus disease (COVID-19) pandemic, can also be a source of stress. Responses that occur in the organism to the stress stimulus are for the benefit of the organism up to a certain level. However, when the duration and intensity of the stress stimulus increase, pathological conditions occur in all physiological systems. Long-term exposure to stress may cause infertility in men by causing decreases in sperm parameters such as sperm quality, sperm concentration, spermatozoid count, and sperm percentage. Various substances are being researched to reduce these adverse effects of stress on the reproductive system. Studies have shown that melatonin has antioxidant, anti-inflammatory, anti-apoptotic, and so on. It shows positive efficacy in male infertility with various mechanisms. This review it is aimed to give information on the effect of stress on the male reproductive system and the relationship between melatonin.

Keywords: Male infertility, Melatonin, Sperm, Stress.

Makale atıf

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INTRODUCTION

Male Reproductive System

In the male reproductive system, the ultimate product for the continuation of the species is the healthy mature sperm cell. Sperm cell production begins with the proliferation and differentiation of spermatogonium, proceeds with the formation of spermatocytes and spermatids, and is completed by transforming spermatids into fertile mature spermatozoa (Kızılay and Barış, 2019). Spermatogenesis has three stages. The first phase is mitosis, in which spermatogonium is reproduced. Secondly, in meiosis, diploid spermatozoa decrease their chromosome number by halving and turning into haploid. Thirdly, in the spermiogenesis stage, spermatids' maturation and differentiation occur. Malfunctions in any of these stages lead to abnormal pathologies such as defective sperm cells or decreased sperm production (Suede et al., 2021). A specific period is required for the completed stages of spermatogenesis. Although this period changes according to the species, it takes approximately 74 days in humans (Neto et al., 2016). As the genetic heredity material is transmitted from generation to generation with sperm cells, healthy sperm production is crucial for the continuation of the species (Hao et al., 2019). Hormonal and autocrine/paracrine factors regulate sperm production and consist of a complex and gradual process in which diploid spermatogonium matures and differentiates to haploid sperm cells (Kızılay and Barış, 2019). Several types of testicular cells and hormonal factors produce mature sperm cells. These cells (Leydig, myoid, Sertoli, somatic, germ, etc.) and the substances produced from these structures constitute the micro testicular environment necessary for spermatogenesis. In order to produce a healthy normal sperm cell, the micro-testicular environment requires optimal conditions (Zhou et al., 2019).

Physio-Anatomical Structure

Testicular germ cells (TGCs) are responsible for maintaining spermatogenesis throughout reproductive activity and originate from primordial germ cells located in the basement membrane of the seminiferous tubule. TGCs have oval nuclei close to the nuclear membrane, dense cytoplasm, a small Golgi apparatus, several mitochondria, and numerous ribosomes. Maintaining the genetic integrity, quality, and function of TGCs is essential for spermatogenetic activities. These cells can differentiate through regeneration, differentiation, or apoptosis. The functions of the Sertoli cells (SCs) play an essential role in deciding which pathway these cells will follow. There is a very tight connection between TGCs and SCs. TGCs activities are likely regulated by paracrine factors released from SCs. In addition, other factors produced by Leydig cells (LCs) and Peritubular myoid cells (PMCs) also play a role in this regulation (Goossens et al., 2006). The spermatogonium produced from TGCs eventually differentiates to mature sperm cells. Spermatogonium are diploid precursors of all other testicular germ cells. Certain local substances also influence the decision of whether these cells either differentiate, regenerate or become apoptotic. For example, glial-derived neurotrophic factor stimulates spermatogonium regeneration, while stem cell factor and retinoic acid stimulate differentiation (Neto et al., 2016).

SCs are another cell group involved in sperm production. SCs create the structural framework and physiological environment necessary for spermatogenesis. These cells are polarised, irregularly formed columnar epithelial cells located in the basement membrane of the seminiferous tubule. Their basal surface is enriched in organelles, while their apical surface is associated with germ cells (Kızılay and Barış, 2019). Approximately 17-20% of the seminiferous tubule epithelium has SCs (Neto et al., 2016). SCs extend from the basement membrane of the seminiferous tubule towards the lumen and provide nutrient support to the seminiferous tubule epithelium, blood testicular barrier (BTB), and TGCs. They are also involved in the phagocytosis of degenerating germ cells. Hormones such as follicle-stimulating hormone (FSH) and testosterone and local factors produced by testicular cells such as myoid and germ regulate the activities of SSCs (Jégou, 1992). For example, testosterone and dihydrotestosterone regulate SCs through androgen receptors. SCs is also a target of FSH. In addition, testosterone activates the androgen receptor in SCs and induces functional pathways necessary for spermatogenesis (Kızılay and Barış, 2019). PMCs are smooth muscle-like cells responsible for contractile activity and propel immature spermatozoa towards the rete testis, the reticular portion of the seminiferous tubules. PMCs have characteristics of both smooth muscles and fibroblasts. In addition to contractility, these cells are involved in testicular development and spermatogenetic

activities. In particular, there is a close collaboration between PMCs and SCs (Díez-Torre et al., 2011).

LCs are polygonal formed testicular cells found in clusters between the seminiferous tubules and blood vessels in the intercellular area. They are believed to be formed by the differentiation of fibroblast-like cells or mesenchymal cells in the testicular intercellular area. LCs is mainly responsible for producing testosterone, small amounts of estrogen, and autocrine/paracrine substances. Luteinizing hormone (LH) binds to its receptor in LCs and causes stimulation of certain enzymes (Star protein, Cytochrome p450) involved in steroidogenesis. This stimulation stimulates an increase in the production of testosterone and estrogen and decreases LCs apoptosis by stimulation of specific signaling pathways. Testosterone regulates the reproductive axis by negative feedback and LCs function by short negative (ultra-fast negative) feedback. Neurotransmitters such as melatonin, epidermal growth factor, atrial natriuretic peptide, ghrelin, and gamma-aminobutyric acid also affect the function of LCs (Neto et al., 2016).

BTB functions as an anatomical and functional barrier that limits the paracellular passage of substances. Certain anatomical junctions close to the basal part between neighboring SCs constitute the BTB. Due to their metabolic needs and immunogenic properties, SCs need a stable microenvironment. BTB separates seminiferous tubule epithelium into two different areas. Thus, two different compartments, basal and adluminal, are formed. Thus, cells in the adluminal compartment are isolated from the external environment. The BTB consists of anatomical structures such as tight junctions, specific basal ectoplasmic extensions, gap junctions, and mammal desmosomes. PMCs and endothelial cells contribute secondarily to this barrier. Local substances such as cytokines and growth factors affect this barrier's structural integrity and function (Neto et al., 2016).

Hormonal Regulation

FSH, LH, and testosterone are responsible for the hormonal stimulation of spermatogenesis (De Krester et al., 1998; Corradi et al., 2016). However, others, such as estrogen and growth hormone, also play a role in spermatogenesis (Tatem et al., 2019). Autocrine/paracrine stimuli such as cytokines and growth factors also play an additional role in the non-hormonal regulation of spermatogenesis (Huleihel and Lunenfeld, 2004). The primary organ of the male reproductive system is the testes in the scrotum. The primary function of the testes is the production of male gametes, with additional functions such as testosterone production. The production of male gametes originates from testicular germ cells, while testosterone is produced by the LCs surrounding the seminiferous tubules. Sperm cells are produced in the seminiferous tubules and then transported to the epididymis, where they are stored (Suede et al., 2021). The process of spermatogenesis is regulated by signals produced by SCs and LCs. In addition to these cells, other testicular cells, such as peritubular cells, macrophages, and vascular tissues, also contribute to spermatogenesis (Konrad et al., 1998). A normal sperm cell is morphologically composed of a head, neck, midpiece, and tail, and the plasma membrane surrounds the sperm cell from head to tail (Bulduk and Cengiz, 2015). Only 300-500 of the 200-300 million sperm passing to the female genital tract can reach the site of fertilization.

Therefore, sperm morphology should not be abnormal for fertilization (Zaneveld et al., 1991; Bulduk and Cengiz, 2015). FSH helps the differentiation of spermatids to sperm cells by stimulating SCs. Although LH is the dominant hormone in sperm production, FSH is required for stimulation and ongoing spermatogenesis. FSH realizes its main effect together with testosterone. FSH indirectly stimulates DNA synthesis in spermatogonium and preleptotene spermatocytes and contributes to the meiosis stage of spermatogenesis (Kızılay and Barıs, 2019). LH stimulates receptors in LCs, and testosterone secretion is realized. Certain gene expressions involved in the testis' steroidogenic and spermatogenetic activities are decreased without LH. At the same time, testosterone replacement can significantly ameliorate the effects of LH deficiency (Griffin et al., 2010). Testosterone is an essential hormone in the proliferation and differentiation of testicular germinal cells, the first step in spermatogenesis. The foremost testosterone-dependent step in spermatogenesis is the spermiogenesis stage, known as the post-meiotic stage, during which long spermatids differentiate. Furthermore, testosterone is highly effective in the survival of spermatocytes and spermatids as it strongly stimulates anti-apoptotic mechanisms (Kızılay and Barıs, 2019). Moreover, the estrogen, growth hormone, and thyroid hormones, involved in testicular metabolic activities, also

play a role in spermatogenesis (Wagner et al., 2008).

Melatonin Synthesis and Pineal Gland

Melatonin is synthesised mainly by pinealocytes, the primary cells of the pineal gland. Melatonin is also produced in small amounts by non-pinealocyte cells such as skin, lens, ciliary body, intestines, testis, ovary, uterus, placenta, oocytes, bone marrow, erythrocytes, platelets, lymphocytes, astrocytes, glial cells, mast cells, and neurons (Tan et al., 2018). In pinealocytes, melatonin is synthesized by a series of consecutive chemical reactions such as hydroxylation, decarboxylation, N-acetylation, and O-methylation of the amino acid tryptophan (Reiter, 1991). Melatonin synthesis is initiated by light information received from the retina. The received light information primarily reaches the suprachiasmatic nucleus (SCN) via the retinohypothalamic pathway, while the postganglionic sympathetic fibers of the superior cervical ganglion terminate in pinealocytes. Norepinephrine released from the nerve terminals of the superior cervical ganglia stimulates pineal cells via β- adrenergic receptors in pinealocytes and accelerates the synthesis of cyclic adenosine monophosphate (cAMP). Thus, tryptophan amino acid is hydroxylated to 5-tryptophan and converted to serotonin. Serotonin is acetylated by N-acetyltransferase (NAT) enzyme and converted into N-acetylserotonin. This stage represents the rate-limiting step of melatonin synthesis. Finally, O-methyltransferase produces melatonin from N-acetylserotonin (Dragojevic et al., 2015). The pineal gland is a small extension of the brain and adheres to the posterior wall of the third ventricle between the posterior and dorsal habenular junction. Although its size and position vary among species, the ratio of the gland to body weight is small in humans compared to other species. In adult humans, this gland weighs 100-180 mg, is 5-9 mm long, 3-6 mm wide, 3-5 mm deep, and is a cone-like gland covered by a pia mater. Embryologically, it originates from the posterior part of the third ventricle and is connected to this area by the pineal body. also, the third ventricle passes into the pineal body to form the epiphyseal pit. Although the pineal gland is small, it is the second organ with the highest blood flow (4 mL/min/g) after the kidneys. Arterial blood circulation is via the medial posterior choroidal branches of the posterior cerebral artery, while venous circulation is via the internal cerebral veins. Although the capillary structure contains a differentiated endothelial structure, it does not contain the blood-brain barrier. In addition, the pineal gland has sympathetic innervation from the superior cervical ganglion. Pinealocytes have nuclei with irregular margins in light microscopy. The gland is also adjacent to numerous synaptic structures involved in axodendritic synaptic communication. After synthesizing melatonin, it is released into the blood or cerebrospinal circulation without storage. Interstitial cells, perivascular macrophages, pineal neurons, and neuron-like cells with paracrine function around pinealocytes contribute to melatonin synthesis (Atasoy and Erbas, 2017). Due to its water and lipid solubility, melatonin easily diffuses into cellular compartments. Once released into circulation, it can easily affect tissues through several fluids such as saliva, urine, cerebrospinal fluid, milk, and semen. Since melatonin is not stored in the pineal gland, plasma melatonin levels accurately represent the activity of the pineal gland. Melatonin secretion peaks at night and is low during the day. In humans, melatonin production reaches its highest levels at 3-6 years of age, while nocturnal melatonin levels decrease to 80% in adulthood. Although plasma melatonin levels vary in humans, some humans have minimal or no nocturnal melatonin secretion (Claustrat and Leston, 2015). Melatonin secretion is circadian, and nightfall is required for maximum secretion. Therefore, melatonin is also defined as the chemical expression of darkness or dark hormone. Light information is processed in retinal ganglion cells and delivered to the SCN via the retinohypothalamic pathway, which is embedded in the optic nerve. The SCN functions as a relay center sending information to the pineal gland. The neural information received through the central and peripheral nervous system is transmitted to the pinealocyte cells via the SCN, and a neural input controls the output of the pineal gland. If this neural input is removed, the pineal gland is inactive. The control of the pineal gland by a neural input from the SCN is not observed in other classical endocrine organs. In addition, negative feedback from peripheral signals may slightly alter melatonin release and rhythm (Reiter, 1991).

Melatonin modulates the target tissue via melatonin receptors, intracellular proteins such as calmodulin or calreticulin, orphan nuclear receptors, or antioxidant systems. Melatonin can bind to different types of melatonin receptors such as melatonin receptor type

1a (Mt1), melatonin receptor type 1b (Mt2), melatonin receptor type 1c, quinone reductase 2 enzyme (Mt3), retinoid-related orphan nuclear hormone receptor (RZR/RORa) and X-linked melatonin-related orphan receptor (GPR50). Mt1 and Mt2 are located on the cell membrane; Mt3 detoxification enzyme; melatonin receptor type 1c in fish, amphibians, and birds; RZR/RORa (retinoid-related orphan nuclear factor) transcription factor; GPR50 (X-linked melatonin-related orphan receptor) acts as an auxiliary of Mt1 (84). Although the interest of melatonin in its receptors is not similar, it shows a strong affinity to Mt1 and Mt2 and a weaker interest in Mt3 (Ng et al., 2017).

Melatonin in Male Reproductive System

Due to its hydrophilic and lyophilic properties, melatonin can diffuse through barriers such as BTB and enter all testicular cells (Yu et al., 2018). Melatonin receptors exist in all testicular cells, especially LCs and SCs. In addition, melatonin has activity on releasing reproductive hormones such as Gonadotropin-releasing hormone (GnRH), FSH, and LH through receptor-mediated mechanisms (Sun et al., 2020). Melatonin regulates the release of gonadotropins by inhibiting voltage-sensitive calcium channels and cAMP accumulation in rat gonadotroph cells (Vanecek, 1999). Melatonin shows a better affinity for LCs than other testicular cells (Baburski et al., 2015). Firstly, the idea that the pineal gland could control puberty was put forward due to early puberty in a child patient with a pineal gland tumor. In the following years, it was stated that melatonin had an inhibitory effect on the reproductive system, but this inhibition ceased with puberty (Reiter, 1998). In recent years, there has also been a significant increase in the number of women who delay childbirth until their late thirties, and melatonin supplements have been used to postpone birth (Meredith et al., 2000). The effect of melatonin on the reproductive system is different according to species and seasons (Yu et al., 2018). Many female mammalian species exhibit annual cycles of fecundity and sterility to provide for the survival of their offspring, planning the optimal time of birth. The essential mechanism mediating this is variation in day length or the photoperiod itself. Mammals with seasonal reproductive cycles are divided into short-day and long-day reproductive species. Sheep, Syrian hamsters, and mink are animals with seasonal reproductive cycles. Neural and endocrine mechanisms underlying seasonal reproduction are investigated by modeling short and long days in laboratory conditions (Tamarkin et al., 1985). According to species, changes in day length and melatonin concentrations affect the male reproductive system. Melatonin decreases androgen receptor and androgen binding protein expression levels in rodents, while it decreases testosterone and androgen levels in Syrian hamsters and reduces testicular size. In addition, melatonin increases testicular development in Sikaa deer, sperm production in silver foxes, and testosterone levels in goats. In sheep, melatonin supplementation of LCs and SCs cultures increases factors such as testosterone, stem cell, and insulin growth, decreasing estrogen levels through Mt1 (Yu et al., 2018). In humans, melatonin inhibits the reproductive axis before puberty, but this inhibitory effect disappears as increasing body mass with puberty decreases plasma melatonin concentration below the critical level (Cebrián-Pérez et al., 2014). In certain male hamsters with seasonal reproduction, during long nights (increased melatonin secretion), disturbances in reproductive function and degeneration of the testes may occur (Yong et al., 2021). In female rats, melatonin treatment inhibited ovarian development and delayed the onset of puberty; in male rats, melatonin treatment decreased testicular size (Kennaway et al., 1997; Edmonds and Stetson, 1994; Edmonds and Stetson, 1995). Serum and seminal fluid melatonin levels have been reported to be found at low levels in infertile men (Frungeri et al., 2017). The melatonin receptors function in humans' hypothalamus and pituitary gland (Weaver et al., 1993; Johnston et al., 2006). Moreover, melatonin plays a role in testicular development through melatonin receptors in the testes (García et al., 2003; Izzo et al., 2010). Melatonin supplementation reduces FSH secretion from SCs in male rats (Lang et al., 1984). In an in vitro study of the fetal rat pituitary gland, it was reported to inhibit LH release (Martin et al., 1982). Hypothalamic neurons in the suprachiasmatic nuclei (SCN) and GnRH releasing neurons are the main targets of melatonin (Wierman et al., 1995). It has been reported that testicular weight decreased by 60% in mice injected with melatonin implants into the GnRH neuronal system in the hypothalamus (Glass et al., 1987). Long-term melatonin use in male mice has been reported to cause decreases in testicular and seminal vesicle volumes and sperm count (Forger et al., 1985).

Melatonin is crucial in photo periodically breeding animals. For example, decreases in gonadotropin inhibitory hormone (GnIH) secretion are found in quails undergoing pinealectomy and orbital enucleation. This decreased GnIH can be restored by exogenous melatonin treatment in a dose-dependent manner (Ubuka et al., 2005). Melatonin is known to regulate GnIH expression in photoperiodic mammals. For example, Siberian hamsters produce more GnIH short days than long days (Ubuka et al., 2012). In rats, melatonin receptor expression is altered after pinealectomy. Production of reproductive hormones in male rats losses its seasonal rhythm after pinealectomy. In addition, pinealectomy changed the melatonin receptor expression type from MT1 to MT2 in the hypothalamus (Liu et al., 2013). Testicular morphological abnormalities and gonadal reduction are observed in male hamsters during long nights (Mason et al., 2010). In addition, melatonin treatment induced significant decreases in the endoplasmic reticulum mass of mouse LCs (Redins et al., 2002). Testosterone production has a complicated release mechanism and is regulated by many factors. However, testosterone production mainly depends on cAMP signaling stimulated by LH (Stojilković et al., 1989). It has been reported that melatonin administration to rat LCs in vitro studies decreases cAMP production dose-dependently (Wu et al., 2001). Moreover, it has been reported that melatonin could also affect testosterone production through cAMP-independent pathways (Stojilković et al., 1989). Since LCs are a higher affinity to melatonin, melatonin plays an essential role in the functions of the male reproductive system (Baburski et al., 2015; Li and Zhou, 2015). Melatonin regulates androgen secretion via the melatonin receptor in LCs (Valenti et al., 1999). It has been reported that 10 mg/kg exogenous melatonin administration for 14 days in mice resulted in the malfunction of seminiferous tubules (Mehraein and Negahdar, 2011). A study in melatonin-treated rats found testicular size reduction and decreased spermatid counts (Rashed et al., 2010). However, despite all these side effects, melatonin has beneficial properties on testicular tissue. Antioxidant substances protect the testes from environmental damage, side effects of cancer, and other toxic molecules (Pieri et al., 1994). Melatonin is a powerful antioxidant (Yang et al., 2014). In a rat study, melatonin significantly ameliorated testicular torsion-induced oxidative stress and lipid peroxidation (Parlaktas et al., 2014). In addition, melatonin treatment decreased the severity of seminiferous tubule damage and increased antioxidant enzyme levels in rats with varicocele (Semercioz et al., 2003). Moreover, melatonin increases the response of SCs to FSH; in this case, testicular damage can be prevented (Heindel et al., 1984). Using melatonin against testicular toxicity in conditions such as testicular torsion or certain anticancer drugs helps protect testicular activities (Lee et al., 2012; Chabra et al., 2013). It has also been reported that melatonin has an antioxidant effect in cases where toxic substances such as cadmium, fluoride, or ochratoxin A increase testicular oxidative stress (Ji et al., 2012; Malekinejad et al., 2011). Moreover, melatonin reduces oxidative damage induced by electromagnetic radiation (Oksay et al., 2012). Testicular tissue is saturated with lipids, and melatonin has been reported to reduce lipid peroxidation (Agil et al., 2011). Melatonin positively affected testicular damage in mice fed a high-fat diet (Zhang et al., 2012). Melatonin protects against sperm cell damage (Awad et al., 2006). For instance, decreased melatonin levels result in abnormal sperm increase (Yie et al., 1999). It has been reported that sperm quality decreases in rams out of the breeding season (Azawi et al., 2012), and melatonin improves semen quality in rams and goats out of the breeding season (Ramadan et al., 2009). However, in a study on men, it was reported that melatonin administration mostly did not cause any change in semen quality. However, in a few males, it caused a decrease in semen quality (Luboshitzky et al., 2002). It has been reported that melatonin administration against testicular ischemia-reperfusion reduces sperm abnormality in rats (Koksal et al., 2012). In invitro studies, it has been reported that melatonin increases mitochondrial activity in sperm cells and increases the percentage of progressive sperm (Du Plessis et al., 2010). It has been stated that this influence of melatonin on sperm quality in vitro conditions is due to the antioxidant effect (Ashrafi et al., 2011). It also shows activity in the male reproductive system through melatonin receptors. (Espino et al., 2011; Reiter et al., 2013).

Stress-Induced Infertility and Melatonin Treatment

Stress is defined as a real or perceived threat to the homeostasis or well-being of an organism resulting from internal or external adverse events (or stressors). Sperm parameters decrease in those exposed to psychological

stress, such as medical students, people who have witnessed the war, men exposed to work stress, and people who have lost a loved one (Nargund, 2015). Although fertility is gradually decreasing in modern societies, many health plans are being made to increase the decreasing population in industrialized countries. More than 186 million people worldwide, mostly in developed countries, have infertility. In the last 40 years, 50-60% decreases in sperm count and quality have been observed. Stress-causing factors such as social failures, economic difficulties, disappointments, and prolonged sitting hours are among the etiological causes of male infertility (Ilacqua et al., 2018). Many clinical studies examining the effects of psychological stress on male fertility have shown that stress is associated with abnormal semen parameters. (Nargund, 2015). In recent years, epidemiological studies have shown that semen parameters decrease in men with high-stress levels (Nordkap et al., 2016; Durairajanayagam, 2018).

Similarly, it is known that there are decreases in sperm concentration and number in depressed male patients (Zou et al., 2018; Zou et al., 2019). In addition, when exposed to stress created by physical stimuli in animals, deterioration in spermatological activities occurs (Guo et al., 2017; Lin et al., 2020). Sperm are overly mobile and provide energy from the abundant mitochondria they have, which causes excessive production of free radicals in the sperm cell. In addition, the fact that the sperm cell is rich in polyunsaturated fatty acids causes it to be sensitive to lipid peroxidation. These two conditions make the sperm cell susceptible to oxidative damage (Lenzi et al., 1996; Darbandi et al., 2018). Studies it has been reported that chronic stress causes oxidative damage and causes disruption in spermatogenetic activities (Liu et al., 2019). In addition, it is mentioned that there is a close relationship between testicular paracrine/autocrine factors such as inflammatory cytokines and spermatogenetic activities (Guazzone et al., 2009). It has been reported that testicular apoptosis increases and testosterone levels decrease in rats' cold water-induced stress model (Juárez-Rojas et al., 2015). In addition, it was reported that the number of testicular apoptotic cells increased in rats administered exogenous dexamethasone (Yazawa et al., 2000).

Although melatonin is safely administered in different doses and times, studies on humans have followed the use of melatonin in stress situations (Guo et al., 2017; Lin et al., 2021; Zhang et al., 2021). For example, It is known that melatonin exhibits anti-inflammatory anti-apoptotic activity in hippocampal inflammation induced by chronic stress (Zhang et al., 2022). It is stated that melatonin shows anti-inflammatory and antioxidant activity in colon inflammation and oxidative stress caused by chronic restraint stress (Lin et al., 2021). Moreover, it has been reported that melatonin treatment showed therapeutic efficacy against disruptions in the intestinal mucosa in mice subjected to chronic restraint stress (Lin et al., 2020). It has been reported that melatonin treatment increases antioxidant activity in the heart in mice under restraint stress (Muqbil et al., 2020). It has been reported that the use of melatonin on metastasis caused by chronic restraint stress in ovarian cancer has a protective effect on ovarian cancer (Bu et al., 2020). It has been reported that using melatonin on gastric lesions induced by stress has a protective effect by eliminating hydroxyl radicals (Bandyopadhyay et al., 2000). In stressful situations, exogenous melatonin acts as an antioxidant, anti-inflammatory, anti-apoptotic, etc., on the male reproductive system. (Kanter, 2010; Asghari et al., 2016; Guo et al., 2017; Sekmenli et al., 2017). Melatonin shows antioxidant and anti-apoptotic effects in heat-induced sperm damage in humans (Zhao et al., 2021). It has been reported that the use of melatonin in temperature-induced testicular damage in wild boars affects the regulation of glucose metabolism in SCs (Deng et al., 2022). Moreover, it has been reported that long-term use of melatonin after heat stress has a healing effect on heat-induced DNA damage and apoptosis and has positive effects on testicular tissue (Guo et al., 2021). In a study in mice, the use of melatonin (10 mg/kg/day) in the damage caused by restraint stress showed an antibiotic, antioxidant, and anti-inflammatory effect, resulting in an increase in testicular tissue protection and spermatological parameters.

CONCLUSION

Melatonin is known to be beneficial in the treatment of male-induced infertility. The literature studies show that using melatonin in male reproductive system pathologies is beneficial in terms of reproductive health. On the other hand, stressful situations appear as an inevitable element of modern life. Physiopathology can be formed in many physiological systems, including the male reproductive system, especially in prolonged exposure to stress. Stress appears to cause infertility in men by causing decreases

in sperm parameters. Although it is known that many substances are effective in the treatment of infertility in men, the substance to be used should be safe and have few side effects. In this sense, melatonin can be considered as a safe molecule. Although the positive effects of exogenous melatonin on the male reproductive system parameters due to stress have been shown in the literature studies through antioxidant, anti-inflammatory and anti-apoptotic mechanisms, extensive research is still needed.

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