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Melatonin and its protective role against male reproductive toxicity induced by heavy metals, environmental pollutants, and chemotherapy: A review

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Abstract: Melatonin, as a ubiquitous indoleamine hormone, is synthesized primarily by the pineal gland. It has diverse biological effects through quite complex mechanisms. More recently, studies have focused on the mechanism of melatonin in anti-reproductive toxicity/damage. Since melatonin possesses strong antioxidant and anti-apoptotic properties, researchers have examined its potential role in protecting against male reproductive toxicity/damage, which may be induced by chemotherapy or environmental toxicants and can lead to male infertility. In this article, recent progress regarding the protective effects of melatonin on male reproductive toxicity/damage is reviewed.

Introduction

Spermatogenesis is a series of cellular processes that result in the production of mature spermatozoa in testis. It occurs in the seminiferous tubules and under the structural and nutritional support of Sertoli cells and the precise regulation of many endocrine factors, including testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen (Clermont, 1967; Hess and França, 2008; Rey, 2003). There are two main types of spermatogenic epithelium: Sertoli cells and germ cells. Sertoli cells are polarized epithelial cells extending from the base of seminiferous tubules to the lumen. They can provide structural and nutritional support to germ cells. Development of germ cells begins with type A spermatogonia, which have self-renewal ability and can differentiate into mature spermatozoa through mitosis and meiosis. Therefore, under normal physiological conditions, endocrine factors, Sertoli cells, germ cells, and other cells work together to maintain mammalian spermatogenesis (Greenbaum *et al.*, 2011; Mruk and Cheng, 2015; Review, 1994).

The testis is one of the most sensitive organs in the body due to its rapidly dividing germinal epithelium through mitosis and meiosis (Lambertini and Fontanella, 2018). Factors that may cause damage to the testis can eventually lead to male infertility. Many drugs, environmental toxicants, and heavy metals or other hazardous factors have been shown to have gonadal toxicity. For example, bisphenol A (BPA), as an environmental toxicant, is one of the endocrine disruptors that probably represents a key point in testis functional alteration (Cheng *et al.*, 2011). The germ cell loss is aggravated by Cadmium (Cd^{2+}) in the seminiferous epithelium and blood–testis barrier (BTB) disruption (Wong *et al.*, 2004; Wong *et al.*, 2005).

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine secreted by the pineal gland, which is involved in many biological activities, including circadian rhythm, redox homeostasis, anti-inflammatory, epigenetic regulation, reproductive physiology, and fetal development (Hardeland *et al.*, 2009; Korkmaz and Reiter, 2007; Tain *et al.*, 2014; Voiculescu *et al.*, 2014). Melatonin is a free-radical scavenger and broad-spectrum antioxidant. It can pass through the blood–testis barrier and enter testis cells (Karaaslan and Suzen, 2015). It exerts its effects via non-receptor activities or receptor-mediated pathways (Reppert, 1997; Reiter *et al.*, 2007). Numerous studies have shown that melatonin plays roles in spermatogenesis and testicular toxicity/damage, highlighting its importance in the male reproductive system (Aitken, 1999; Deng *et al.*, 2018; Navid *et al.*, 2017a; Navid *et al.*, 2017b;

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Reiter, 1991; Dragojevic Dikic *et al.*, 2015; Vakifahmetoglu-Norberg *et al.*, 2017; Zhang *et al.*, 2019a).

Male reproductive health and fertility decline may be related to the presence of toxic chemicals in the environment. Melatonin has become a common reagent for the protection of male fertility, which can prevent the male reproductive toxicity/testis damage caused by environmental pollutants, such as heavy metals. Here, we review the findings of melatonin on male reproductive toxicity/testis damage, and, in particular, on its protection against reproductive toxicity induced by factors such as heavy metals, environmental toxicants, and chemotherapy.

The Roles and Functions of Melatonin in Male Reproduction

Introduction of melatonin on male and female reproduction

Melatonin has important effects on the male and female reproductive systems, including both spermatogenesis and folliculogenesis (Dragojevic Dikic *et al.*, 2015). In the male reproductive system, melatonin mainly affects reproductivity in three ways (Fig. 1). First, it regulates the secretion of gonadotropin-releasing hormone (GnRH) and LH hormones through the hypothalamic–pituitary–gonadal axis. Second, it regulates testosterone synthesis and testicular maturation. Third, as a free radical scavenger, it can prevent testicular damage caused by environmental toxins, heavy metals, or inflammation (Yu *et al.*, 2018).

The molecular mechanism of melatonin and its receptor

Melatonin receptor is widely distributed in the body, including the immune and endocrine systems, cardiovascular tissues, male reproductive system, and even the gastrointestinal tract and skin (Slominski *et al.*, 2012). In different cell types of animal and human, melatonin has specific receptors and intracellular targets, which can then regulate many physiological functions and modify the activities of adenylate cyclase, guanylate cyclase, and phospholipase C. Specifically, membrane melatonin receptors 1 (MT1) and 2 (MT2) have specific short amino acid sequences (Drew *et al.*, 2001; Ekmekcioglu, 2006). Both receptors show high amino acid sequence homology and can inhibit cyclic AMP production. Except for MT1 and MT2, retinoid acid receptor-related orphan receptor A (ROR) has been identified in various cell types of animal and human (Sanchez-Barcelo *et al.*, 2016). In addition, MT3, a quinone reductase 2, plays an important role in scavenging free radicals in various tissues of hamster and rabbit. However, MT3 has not been found in humans (Smirnov, 2001).

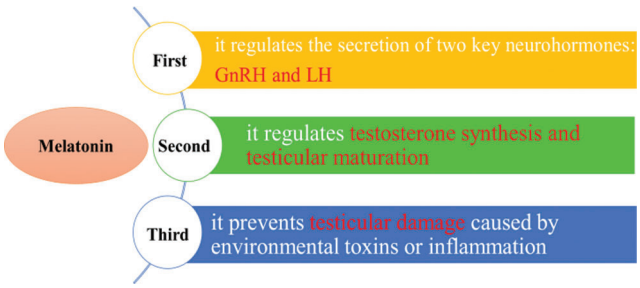

FIGURE 1. The main roles and functions of melatonin in male reproduction (Li and Zhou, 2015; Yu *et al.*, 2018).
GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone.

The multiple and complex physiological effects of melatonin are mediated by interaction with membrane MT1, MT2 and MT3 receptors or indirectly with nuclear orphan receptors of the ROR alpha/RZR family (Slominski *et al.*, 2012). For example, the MT1 receptor modulates reproductive and metabolic functions in Leydig cells (Dubocovich and Markowska, 2005; Slominski *et al.*, 2012). Usually, the MT1 receptor and its physiological functions are combined with MT2, which has been detected in testicular tissue (Dubocovich, 2007; Dubocovich and Markowska, 2005). Melatonin can also bind to ROR (RORα1 and RORα2) and RZR, which are involved in several biological processes, including cell proliferation (such as that of spermatogonial stem cells) and differentiation (such as the differentiation of spermatogonia into spermatids) in seminiferous tubules (Evans, 2005; Reiter *et al.*, 2010; Yu *et al.*, 2018).

The functions of melatonin in male reproductive system

In the male reproductive system, reactive oxygen species (ROS) and reactive nitrogen species (RNS) play important roles in spermatogenesis. However, overproduction of ROS and RNS affects spermatogenesis and hormone secretion (Allegra *et al.*, 2010). Melatonin acts as an anti-oxidant and anti-apoptotic agent and reduces the production of ROS and RNS via non-receptor-mediated pathways (Bałabusta *et al.*, 2016; Fischer *et al.*, 2013; Galano *et al.*, 2011; Bejarano *et al.*, 2015; Karbownik *et al.*, 2001; Reiter *et al.*, 2016). Furthermore, melatonin scavenges excessive ROS and RNS via melatonin receptor-independent mechanisms (Salehi *et al.*, 2019).

Current research status and application prospect of melatonin in anti-reproductive toxicity

The effects of MLT on the male reproductive system have been previously reviewed, it is recognized to affect male reproductive toxicity induced by heavy metals, environmental pollutants, and chemotherapy.

Melatonin and heavy metal-induced reproductive toxicity

Heavy metals, such as Cd^{2+} and lead (Pb), are widely used in industrial and agricultural practices and can cause reproductive toxicity (Fig. 2) (Ding *et al.*, 2018). Cd^{2+} is a non-biodegradable metal that is harmful to human health. It can accumulate in tissues and organs, increase FSH and LH levels, and disrupt the male reproduction system (Szczerbik *et al.*, 2006). Melatonin, as an antioxidant and free radical scavenger, reduced Cd^{2+}-induced changes in the reproductive system (Drąg-Kozak *et al.*, 2018). Another study demonstrated that melatonin ameliorated Cd^{2+}-induced DNA damage and inhibited autophagy in spermatozoa through the ATM/AMPK/mTOR signaling pathway (Li *et al.*, 2017). With the development of the global food industry, Pb toxicity has become a major international public health problem. Pb can induce lipid peroxidation, decreased levels of superoxide dismutase, catalase, peroxidase, and glutathione peroxidase. However,

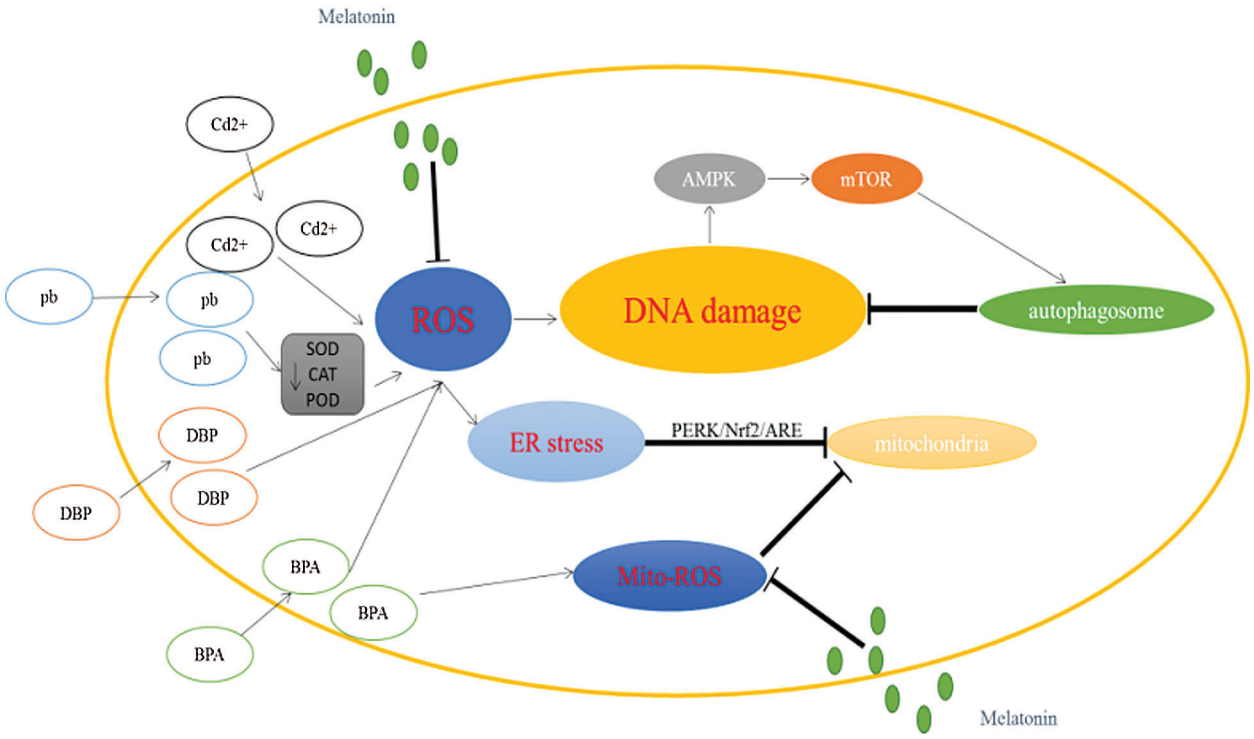

FIGURE 2. Role of melatonin in heavy metal-induced and environmental toxicant-induced reproductive toxicity (Bazrgar *et al.*, 2015; Park *et al.*, 2018; Wu *et al.*, 2013; Zhang *et al.*, 2019a).
Cd^{2+}: cadmium; Pb: lead; DBP: dibutyl phthalate; BPA: bisphenol A; SOD: superoxide dismutase; CAT: catalase; POD: peroxidase; ROS: reactive oxygen species; ER: Endoplasmic reticulum; mito: mitochondria; AMPK: AMP-activated protein kinase; PERK: protein kinase RNA (PKR)-like ER kinase; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element.

melatonin was found to reduce the oxidative damage induced by maternal Pb exposure (Bazrgar *et al.*, 2015). Pb also causes male gonadotoxicity through oxidative stress and endocrine mechanisms, and melatonin can improve semen parameters and some biochemical markers in Pb-exposed males (Olayaki *et al.*, 2018).

Melatonin and environmental toxicant-induced reproductive toxicity

Many environmental toxicants, such as dibutyl phthalate (DBP), are found to increase germ cell apoptosis and induce male reproductive toxicity (Fig. 2) (Zhang *et al.*, 2016). DBP is shown to stimulate intracellular ROS production associated with mitochondria-related damage, endoplasmic reticulum stress, and mitochondrial-dependent apoptosis (Zhang *et al.*, 2019a). Melatonin can protect against the DBP-induced ROS-related mitochondrial damage and apoptosis through phosphorylated ERK and the Nrf2 (NF-E2 related factor 2)/ARE (antioxidant response element) antioxidant pathway (Zhang *et al.*, 2019a). BPA is a well-known endocrine-disrupting chemical that has a widespread distribution in humans. The possible genotoxicity of BPA has been reviewed (Wu *et al.*, 2013). Due to its chemical similarity to diethylstilbestrol, BPA may induce the accumulation of DNA damage in germ cells via oxidative stress (Wu *et al.*, 2013). Melatonin therapy may be the most effective way to prevent the potential genotoxicity caused by occupational or environmental exposure to BPA (Park *et al.*, 2018; Wu *et al.*, 2013). Declined male fertility is also suggested to be related to electromagnetic fields. Electromagnetic field exposure may reduce the melatonin levels and have deleterious effects on the reproductive system (Kumar *et al.*, 2012). Ochratoxin A exhibits toxic effects on testes, and melatonin provides a degree of protection against its toxic effects in rats (Malekinejad *et al.*, 2011). Air pollution has been clearly demonstrated to be associated with male fertility (Jeng and Yu, 2008; Santi *et al.*, 2018). Air pollutants (PM2.5, PM10, SO_2, NOx, O_3, and PAHs) may impact semen parameters, DNA fragmentation, telomere length, sperm aneuploidy, and the level of reproductive hormones (Jurewicz *et al.*, 2018; Miri *et al.*, 2019; Santi *et al.*, 2018). Melatonin may play a crucial role in preventing the potential reproductive toxicity caused by air pollutants (Ji *et al.*, 2018).

Melatonin and chemotherapy-induced reproductive toxicity

At present, cancer is one of the major diseases affecting human health (Ferlay *et al.*, 2015). Unfortunately, many anti-cancer drugs have adverse effects on the reproductive system. In particular, chemotherapy can alter the levels of hormones and sperm quality, leading to reduced fertility or infertility (Haghi-Aminjan *et al.*, 2017). Melatonin may have protective roles in busulfan-induced testicular damage and testicular torsion, suggesting that melatonin may provide effective therapy for cancer patients receiving chemotherapy (Deng *et al.*, 2018; Mohammadghasemi *et al.*, 2010). Melatonin also directly regulates testicular androgen production and secretion by binding to the MT1 receptor in testes (Deng *et al.*, 2018; Reiter, 1991).

Previous studies have shown that melatonin plays an important role in the regulation of testicular development and male reproduction (Alagbonsi *et al.*, 2016; Mirhoseini *et al.*, 2014). Melatonin protects testicular damage by improving the antioxidant capacity and inhibiting the inflammatory response via Nrf2/hemeoxygenase-1 and nuclear factor-κB/inducible nitric oxide synthase pathways (Guo *et al.*, 2017; Wang *et al.*, 2018). It has radioprotective effects against 60 Co γ-ray-induced testicular injury, indicating that it may benefit the male reproductive system during radiotherapy (Khan *et al.*, 2015). Cyclophosphamide is an anticancer drug with side effects of testicular injury that can cause infertility. Melatonin is reported to have protective effects on the diameters of seminiferous tubules and the Johnsen's Testicular Score (Torabi *et al.*, 2017).

Many studies have examined the effect of melatonin on reproductive systems during chemotherapy-induced reproductive toxicity. Melatonin serves as a safe natural compound that can be used as an adjuvant drug to protect patients from such reproductive toxicity (Ghobadi *et al.*, 2017). One study reported that melatonin effectively protected spermatogonia from chemotherapy and oxidative stress via the reduction of ROS (Fig. 3) (Zhang *et al.*, 2019b). *In vitro* experiments also showed that melatonin strongly attenuated chemotherapy-induced cytotoxicity and apoptosis via the MT3 receptor (Pariente *et al.*, 2017). Understanding the mechanisms and properties of melatonin may provide important means for the protection of male fertility in the clinical setting. However, it has been generally accepted that melatonin has bilateral effects on reproductive cells. For example, although melatonin protects many cells and the reproductive system via reducing oxidative stress and apoptosis, and regulating mitochondrial function, and sexual hormone (FSH, LH, and testosterone) levels, it also causes anti-proliferative effects (Haghi-Aminjan *et al.*, 2017).

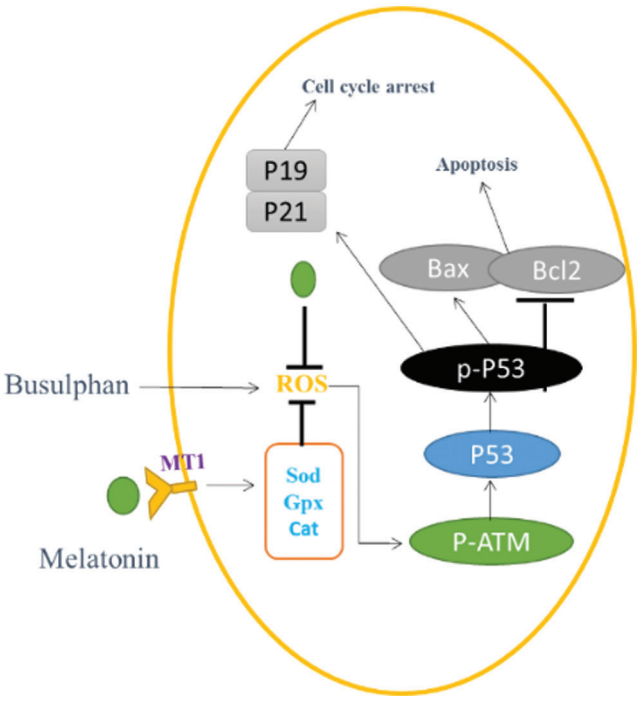

FIGURE 3. Model for melatonin-induced protection of spermatogonia during chemotherapy (Zhang *et al.*, 2019b). CAT: catalase; SOD: superoxide dismutase; Gpx: glutathione peroxidase; p-ATM: ATM serine/threonine kinase.

TABLE 1

Effect of melatonin on male reproductive system

Types	Species/ cells	Melatonin effects	References
Melatonin and heavy metals on reproductive toxicity	Fish	*on fish reproduction induced by environmental Cd^{2+} contamination*	(Drąg-Kozak *et al.*, 2018)
	Mouse	*ameliorated DNA damage, and inhibited autophagy induced by Cd^{2+}*	(Li *et al.*, 2017)
	Rat	*increased sperm parameters and some biochemical markers in lead (Pb)-exposed male system*	(Olayaki *et al.*, 2018)
Melatonin and environmental toxicants on reproductive toxicity	Rat/ Porcine	*may be the most effective way to prevent potential genotoxicity of BPA occupational or environmental exposure*	(Park *et al.*, 2018; Wu *et al.*, 2013)
	Human	*electromagnetic field exposure also reduced the level of melatonin*	(Kumar *et al.*, 2012)
	Pigs	*plays a crucial role for preventing the potential reproductive toxicity caused by air pollutants*	(Ji *et al.*, 2018)
Melatonin and chemotherapy-induced reproductive toxicity	Human	*effectively protects spermatogonia from the stress of chemotherapy and oxidation via eliminating reactive oxidative species*	(Zhang *et al.*, 2019b)
	HeLa cells	*strongly enhances chemotherapeutic-induced cytotoxicity and apoptosis*	(Pariente *et al.*, 2017)
	Human	protects people undergoing cyclophosphamide-induced testicular toxicity against reproductive toxicity	(Ghobadi *et al.*, 2017)
	Human/ animals	*has bilateral effects on reproductive cells*	(Haghi-Aminjan *et al.*, 2017)

Note: Cd^{2+}: cadmium; Pb: Lead; BPA: bisphenol A; EMF: electromagnetic fields.

Conclusions

Melatonin is extremely beneficial in protecting male reproduction from environmental toxicants (e.g., DBP and BPA) as well as from reproductive toxicity caused by chemotherapy and air pollutants. Melatonin also directly regulates the normal testicular function and the secretion of testosterone by binding to its specific receptors.

Collectively, the literature reports the crucial roles of melatonin in preventing testicular damage and reproductive toxicity (Tab. 1). Therefore, further studies are needed to understand the more detailed interaction mechanisms between melatonin and the male reproductive system and to clarify the beneficial effects of anti-reproductive toxicity/damage in clinical practice.

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Availability of Data and Materials: The datasets used or analyzed during the current study are available from the corresponding authors on reasonable request.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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