Review

The protective effects of melatonin on organisms against the environmental pollutants of heavy metal and non-metal toxins

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ABSTRACT

Metal and non-metal toxins are primarily derived from the human industrial and agricultural activities. These toxins have substantially polluted our ecosystem and become a major threatening factor to our health. Metal or non-metal pollutants are highly toxic because they interact with biological macromolecules including DNA, proteins and membrane to induce oxidative stress. If they are not properly handled, these toxins will inevitably cause organ and tissue injuries in both animals and plants. To identify the effective remedies to detoxify these toxins becomes the urgent agenda for researchers. Accumulated evidence indicates that melatonin may be a suitable molecule for this purpose. Melatonin, a naturally occurring antioxidant, directly scavenges ROS or upregulates expressions of many antioxidant enzymes to indirectly reduces ROS. In addition, it also promotes the excretion of these metal or non-metal toxins from the body. The multiple protective mechanisms of melatonin effectively suppress the oxidative stress induced by the metal or non-metal toxins in animals or plants. Melatonin is an environmental-friendly molecule with low or none toxicity to animals or plants. It is a promising molecule which can be used to detoxify the environmental pollutants.

Key words: melatonin, environmental toxins, oxidative stress, heavy metals, pollution.

1. INTRODUCTION

Melatonin, or N-acetyl-5-methoxytryptamine, is a physiologically diverse indolamine found in many organisms. In vertebrates, melatonin is mainly secreted by the pineal gland. However, it is

also synthesized possibly in the mitochondria of every cell (1). In vertebrates, melatonin has been detected in the retina, bone marrow cells, platelets, gastrointestinal tract, lymphocytes, brain and liver (2, 3). In plants, melatonin is present in all parts of them including the roots, stems, leaves, flowers, fruit and seeds, but the specific cellular organelles that produce melatonin remain to be confirmed which may be chloroplasts (4, 5). The broad biological roles of melatonin are in part mediated by G protein-coupled receptors (GPCRs), while other actions are believed to be receptor independent (6, 7). Melatonin membrane receptors (MR) were classified into three subtypes, MT1, MT2 and MT3, at the International Union of Basic and Clinical Pharmacology meeting in 1998. In animals, melatonin has major role in regulating circadian rhythms under physiological conditions (8). However, melatonin also has many other important functions, such as the antioxidant activity (9), enhancing immunity (10), promoting successful male and female reproduction (11, 12), inhibiting tumor progression (13) and preserving gastric mucosal function (14). In plants, melatonin mainly regulates circadian rhythms (15), plant growth (16) and improves their resistance to bio- and abiotic stresses (17). Many of these stressors come from the environmental pollution. Thus, the comprehensive analyses of the protective roles and mechanisms of melatonin on organisms against environmental pollutants are crucial and it is a rational for this review.

Humans, other animals and plants are exposed to environmental toxins through various routes. Upon entering organisms, these toxic substances are metabolized and often accumulated to result in a variety of adverse effects, including neuronal, reproductive, gerontologic and cardiovascular toxicities. Based on their chemical properties, common environmental toxins can be classified as metal or non-metal agents. The most often encountered toxic metals are cadmium (Cd), mercury (Hg), manganese (Mn), chromium (Cr), lead (Pb), and arsenic (As). Strictly, As is not metal *per se* but its properties are similar to those of metals, thus, it is included in the category of metals in this review. In addition to the metals, several non-metal substances also discussed due to their environmental toxicities. These substances include 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), formaldehyde (FA), cyanide, and polychlorinated biphenyls (PCBs). The continuously increased presence of these toxins in the environment is a severe global problem associated with socioeconomic development. To cleaning up of them is a daunting task of generations. However, at the moment, self-protection is a feasible strategy to be taken. Thus, it is necessary to understand the mechanisms underlying the toxicity of these substances as well as the corresponding prevention and treatment methods. For these purposes, the protective effects of melatonin on these metal and non-metal toxins will be discussed in the current review.

Most environmental toxins generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), consume glutathione, and induce lipid peroxidation (LPO). All of these lead to oxidative stress and various tissue or organ damage including neurons, ovary, testes, liver, kidney, heart and even carcinogenesis (20-24). Melatonin, a potent free radical scavenger and antioxidant is frequently reported to inhibit the adverse effects of environmental toxins (18, 19). This review will focus on the protective mechanisms of melatonin on environmental toxins and helpfully it will stimulate research enthusiasm on this subject.

2. PROTECTIVE EFFECTS OF MELATONIN ON TISSUE OR ORGAN INJURIES ASSOCIATED WITH HEAVY METAL TOXICITIES

In this section, the focus is given to the protective effects and the potential mechanisms of melatonin on heavy metal induced tissue and organ injuries.

2.1. Melatonin and Cadmium (Cd).

Cd is a heavy metal of environmental toxin and it is also classified as a human carcinogen. The common exposure routes of Cd include occupational contact, dietary consumption and cigarette smoking (25). In animals, excessive Cd exposure induces a variety of adverse effects, including hepato- (20), neuronal (23), reproductive (21), immune- (26), carcinogenic (27) and cardiac toxicities (22). Studies have shown that intake of antioxidants of spirulina, lipoic acid, melatonin or N-acetylcysteine reduces the risks associated with Cd exposure (28). Among these antioxidants, melatonin is the most investigated one for detoxifying the Cd. The protective mechanisms of melatonin on Cd toxicity involve several pathways. For example, Cd accumulation in the liver induces oxidative damage and inflammation, while melatonin confers protection against Cd-induced hepatic inflammation and hepatocyte death by inhibiting the thioredoxin-interacting protein (TXNIP)-NOD-like receptor 3 (NLRP3) inflammasome pathway (20, 29). Cd-induced neurotoxicity is associated with the abnormal mitochondrial dynamics; melatonin prevents Cd-induced neurotoxicity by blocking the mitochondrial fusion and fission imbalance (30) and in addition, melatonin also enhances the transcription factor EB (TFEB)-mediated autophagy to reduce Cd-induced neurotoxicity (23). In the *in vivo* condition, Cd causes carcinogenesis in the uterus and mammary glands. This action is made by Cd to mimic estrogen's activity and to initiate oxidative stress (25). Melatonin inhibits Cd-induced cell proliferation by inhibiting estrogen receptor alpha (ERα) expression and downregulates Cd-induced transcription of estrogen response elements (ERE) and AP1-containing promoters; thus, inhibits the carcinogenesis induced by the Cd. This antagonistic activity of melatonin on estrogen receptor highly indicates its potentially therapeutic utility in breast cancer (18). Cd can cause systemic high blood pressure by enhancing LPO; however, under many situations, melatonin effectively prevents LPO formation, thereby reducing the toxicity of Cd (31, 32). As a transition metal, Cd has the trend to participate many oxidative reactions and generates large quantity of ROS which lead to oxidative damages in variety of organs including heart (22), immune organs (26), testis (27) and circadian rhythm disruption (34). All of these damages induced by Cd are protected by the antioxidant capacity of melatonin (33). An extensive study has addressed the protective effects of melatonin on the multi system oxidative damages induced by the Cd (35).

2.2. Melatonin and Mercury (Hg).

Hg is present in a wide range of inhabitant and industrial environments. It is difficult to avoid contact with Hg due to the fact that this metal can evaporate into air. Hg is a typic heavy metal which promotes ROS generation in our body (36, 37). Thus, Hg causes gerontological (37), neuronal (38), endocrine (19), cardiovascular (39), and nephron toxicities (40). In each of these conditions, melatonin has the profound protective effects which are also attributed to its antioxidative capacity. For example, a very low dose of Hg does not alter the sperm viability, but it has already disrupted the antioxidant defense system of the sperms (41). Hg accumulation in tissue depletes glutathione and induces oxidative stress leading to lipid and DNA damage. Melatonin effectively protects against Hg-induced oxidative damage in renal, hepatic, pulmonary and brain tissues (42). It has observed that a long-term of Hg exposure to thyroid gland of rat causes decreased synthesis of antioxidant enzymes and other metabolic enzymes in this gland and melatonin application protects against these alterations occurring in thyroid gland (19). Hg toxicity causes oxidative stress which elevates left ventricular end-diastolic pressures and finally, results

in cardiovascular damage. This Hg-induced myocardial oxidative injury can be prevented by melatonin treatment in rats (39). The protective effect of melatonin is also observed in nephrotoxicity of Hg (40). The stress proteins are the reliable indicators of renal damage, and their expression patterns are associated with specific mechanism of each metal (36). Hg-exposed rats suffer from acute renal injury; therefore, the stress proteins are upregulated in a dose-dependent manner to manage restoring the functions of cytoskeleton, mitochondria and nuclei. Treatment with melatonin modulates stress protein expression, thereby promoting renal tubule recovery in Hg exposed rats (36).

2.3. Melatonin and Manganese (Mn).

Mn is an essential micronutrient in humans; it is critical for normal physiological functions such as development, metabolism and antioxidant defense. However, excessive exposure or intake of Mn is harmful, leading to adverse effects such as oxidative stress (43), aggravation of mitochondrial dysfunction (44), enhancement of autophagy (45), promotion of apoptosis (46), and, ultimately, development of neurodegenerative diseases. Mn is present in the natural environment and its pollution is mainly made by human activities. The routes of Mn into our bodies are primarily via diet, breathing and skin contact (47). The specific mechanism by which Mn produces toxicity remains to be clarified. However, oxidative stress is considered as one of the important factors. It was reported that Mn accumulation in astrocytes suppressed the ability of astrocytes to promote neuronal differentiation while a classic antioxidant glutathione alleviated the toxic effects of Mn on the astrocytes (48). This observation was also confirmed by melatonin treatment which detoxified the toxicity of Mn on astrocytes via increasing glutathione levels (48). In addition to the astrocytes Mn also causes motor neuron dysfunction related to oxidative stress and dopaminergic neurodegeneration. Melatonin pretreatment attenuates this dysfunction through antioxidant mechanisms and preservation of dopaminergic neurons (49). Furthermore, melatonin treatment reduced Mn- and/or lipopolysaccharide (LPS)-induced microglial activation, LPO production and reverses intracellular glutathione depletion (50). The similar effects was observed in the spontaneous motor system, melatonin prevents the reduction in spontaneous motor activity (SMA), LPO production and malondialdehyde (MDA) formation caused by Mn (51). The molecular mechanism exploration indicated that melatonin activated nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream enzymes to reverse Mn-induced oxidative damage (50).

2.4. Melatonin and Chromium (Cr).

Cr, an essential micronutrient, is required to maintain optimal insulin activity and normal carbohydrate and lipid metabolism (52). However, Cr(III) and Cr(VI) are well-known occupational and environmental carcinogens (53). Both of them can easily enter into human body and cause damages of liver, kidneys and other internal organs. As a transition mental, Cr(III) and Cr(VI) are active to initiate oxidative reactions and generate ROS. Cr(III) has been reported to cause cellular oxidative damage and carcinogenesis (24). Interestingly, Cr(III) also possesses some novel therapeutic potency on diabetes and obesity (52). Cr(VI) is often associated with oxidative hepatotoxicity (54), apoptosis (55), cytotoxicity (56) and DNA damage (57). As a potent free radical scavenger, melatonin not only detoxifies hydroxyl radical and hydrogen peroxide generated by Cr(III) and Cr(VI), but also promotes ions binding to them to form the harmless Cr-compounds (58).

As noted, the biological effects of Cr(III) seem complicated by its dual roles. It is a strong oxidative agent to damages multiple tissues, but it also exhibits beneficial effect on diabetes. It appears that the anti-diabetic effect of melatonin has certain association with Cr(III). For example, Melatonin's beneficial effect on the Zucker's diabetic fat (ZDF) rats is attributed to the enhancement of plasma Cr concentration of these rats. This novel observation may provide a new therapeutic strategy for diabetes (59). Cr(III) also exhibits antidepressant-like effect similar to melatonin (52). Indole-3-propionic acid (IPA) is a melatonin structure similar molecule with antioxidant and free radical scavenging abilities. When the presence of hydrogen peroxide (H_2O_2), the Cr(III) catalyzes H_2O_2 to form hydroxyl radical which damages fluidity of rat microsomal membranes, while pretreatment with IPA prevents these membrane changes (57). Hydroxyl radicals generated by Cr(III)-mediated Fenton-type reaction damages DNA to form 8-hydroxydeoxyguanosine (8-OH-dG, an oxidative DNA damage marker) and this is main mechanism that Cr(III) causes DNA mutations and carcinogenesis (53, 60). The use of melatonin significantly reduces the incidence of Cr(III)-related carcinogenesis (61). Melatonin not only acts on the Cr(III) but also exhibits protective effects on Cr(VI)-induced various types of cellular, tissue and organ injuries. For example, Cr(VI) exposure leads to cytological damage in hepatic tissue and promotes cell necrosis/apoptosis and melatonin treatment counteracts these damages and also preserves the normal insulin and glucose levels (54). Cr(VI) exposure in male mice destructs the testicular histology and leads to germ cell apoptosis while cotreated Cr(VI) with melatonin preserves the normal spermatogenesis and male fertility (55). Melatonin directly scavenges ROS and indirectly stimulates the activities of a variety of antioxidant enzymes to further strengthen its antioxidant capacity (62, 63). These duel functions of melatonin make it effectively protecting cells from Cr(VI)-induced DNA strand breaks, cytotoxicity and LPO formation and also elevates the levels of vitamin E and C , catalase (CAT) activity and reduces highly toxic hydroxyl radicals (24, 56).

2.5. Melatonin and Lead (Pb).

Pb is a highly toxic heavy metal which causes many adverse health events when it is accumulated in tissues and organs of organisms (64). Pb currently is among the most important environmental toxins in some regions. Its toxicity is manifested by an imbalance between pro-oxidant and antioxidant system in the body and this is probably associated with Pb's high affinity to bind with sulfhydryl groups of functional proteins, such as enzymes (65). Pb can cause acute toxicity as well as the chronic toxic effects. The chronic toxicity of Pb is more profound than that of its acute toxicity. This is because the chronic damages caused by Pb are difficult to recover after prolonged exposure to this metal (65). Pb toxicities vary including neurotoxicity (66), genotoxicity (67), renal damage (68), oxidative stress, DNA damage, and apoptosis (69). The toxicity of Pb on neuron system is profound and its exposure, especially to children, lead to memory (70) and motor deficits (66).

Pb exhibits a unique characteristic which influences the metabolism of metals including itself. It downregulates the expression of metal transporters in metal excretory organs (i.e., the liver and kidney) and this, in turn, promotes accumulation of Pb or other toxic metals in organs (64, 71). This feather of Pb can magnify the toxicities of other heavy metals in organisms. An important mechanism to retard the Pb toxicity is that melatonin upregulates the expression of metal transporters and thus, increases Pb excretion and inhibits its accumulation (64, 71). The protective effects of melatonin on Pb-induced neurotoxicity, genotoxicity and gonadal toxicity are probably

mediated by this mechanism or other mechanisms (67, 72, 73). As we mentioned that nervous system is a primary target of Pb. Even the low-level Pb exposure can cause neuronal damage due to the high sensitivity of neuron to the Pb. The Pb induced neuronal toxicity is manifested by the excessive neuronal apoptosis and this can be effectively prevented by melatonin treatment (72). In addition to reducing the Pb accumulation, the antioxidative activity of melatonin is another important mechanism to detoxify Pb exposure (67). Pb-induced male gonadal toxicity is mediated by excessive oxidative stress that is prevented or alleviated by melatonin in a dose-dependent manner (73). The oxidative stress caused by Pb is indicated by increases in LPO production and thiobarbituric acid reactive substance but reduced activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD) in cerebellum of rat exposed to Pb, thereby impairing the motor activity of this animal. Melatonin alleviates this Pb exposure-induced motor deficits via its antioxidant activity (66). The similar protective effects of melatonin are observed in hippocampal memory deficits caused by joint exposures of Pb and ethanol (70).

Most forms of oxidative stress are characterized by the simultaneous elevation of ROS and RNS. However, in Pb-induced oxidative stress is, somehow, associated with decreased nitric oxide (NO) levels in the kidneys. Melatonin reduces Pb-induced oxidative stress and nephrotoxicity but without significant modification of nitric oxide content. It is likely that the NO alteration plays a limited role in Pb induced nephrotoxicity in kidneys (68).

The protective effect of melatonin against Pb toxicity seems to depend on the doses of Pb. Melatonin can effectively protect against the tissue injury induced by low-dose of Pb exposure, but it is less effective for the high-dose of Pb-induced toxicity (69). A chronic melatonin administration has also failed to reverse high dose of Pb-induced cognitive deficits in rats. Moreover, this study also indicated that melatonin might impair long-term potentiation (LTP) in the dentate gyrus (DG) of the hippocampus and led to the learning and memory deficits (74). This observation has not confirmed by others yet.

2.6. Melatonin and Arsenic (As).

As is a naturally occurring metalloid that exists in the environment in both organic and inorganic forms; it is one of the most dangerous environmental toxins for human health (75). Due to environmental pollution and industrial development, human exposure to As is gradually increased. As can inhibit activities of enzymes, damage protein structures and induce ROS production to cause oxidative stress, which is detrimental to organs and tissues (76, 77). As also causes various other adverse effects, including inflammation (78), apoptosis (79), metabolic disorders (80), genotoxicity (81), and carcinogenesis (82). All of these adverse effects caused by As can be protected by melatonin. For example, the As exposure to rats damages their central nervous system by the excessive production of ROS, NOS and proinflammatory cytokines while melatonin treatment suppresses the oxidative stress and proinflammatory cytokines; therefore, restores disturbed neurological functions (83). As also causes nephrotoxicity by the mechanism that it initially causes mitochondrial dysfunction, in turn, triggers a cascade of inflammation and cell death mediated by tumor necrosis factor α (TNFα) and disturbing glucose uptake, and finally destroys the function of kidneys. Melatonin treatment breaks this pathway by inhibition of TNFα expression and successfully alleviates As-induced nephrotoxicity (78). In reproductive system, melatonin protects against As-induced testicular damage, as indicated by reduced morphological alterations and germ cell apoptosis (79).

Interestingly, arsenic trioxide (ATO), a compound that contains As, is a traditional Chinese

medicine and it is used mainly for the treatment of various cancers even its toxicity has long been a biomedical concern (82). Regarding to its toxicity, ATO is easily absorbed by the digestive system and accumulated in liver to reduce the activities of several antioxidant enzymes including SOD, GPx and CAT, thus, results in pathological alterations of liver. Melatonin reduces ATO-induced liver injury by upregulating the PI3K/AKT pathway to upregulate Nrf2 expression (62). It is well known that activating transcription factor 2 (ATF2) involves transcriptional responses leading to cell migration and malignant tumor progression and melatonin significantly downregulates ATF2 expression to suppress the carcinogenesis (84). Thus, melatonin facilitates the ATO induced toxicity on the cancer cells to improve the anticancer effects of ATO. It is observed that ATO treatment induces apoptosis in the estrogen receptor (ERα)-positive Michigan Cancer Foundation-7 breast cancer cell line while melatonin cotreated with ATO significantly upregulates DNA damage-inducible transcript 4 expression and inhibits the p38/JNK pathway in human breast cancer cells compared to the ATO treatment alone and enhances ATO-induced apoptotic cell death. Reports have documented that the combined use of melatonin and ATO may be a new therapeutic strategy for breast cancer (82, 85). Currently, the mechanisms of the differential effects of melatonin on the ATO induced toxicities in normal cells and cancer cells are not clarified. As we know that melatonin metabolisms are quite different in normal cells compared to the cancer cells. It has been reported when melatonin is metabolized to form N-acetylserotonin in mitochondria, this metabolite significantly suppress tumor growth, but without obvious effects on the normal cells (86). Actually, the major sites for melatonin synthesis and metabolism are mitochondria (87). Thus, different melatonin metabolism in the normal and cancer cells may explain this phenomenon.

3. PROTECTIVE EFFECTS OF MELATONIN ON TISSUE AND ORGAN INJURIES ASSOCIATED WITH NON-METAL TOXINS

In this section the focus is given to the protective effects of melatonin on the non-metal toxins.

3.1. Melatonin and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

TCDD is a highly toxic environmental chemical with multiple adverse effects, including impairment of fertility, inhibition of lymphocyte function, and disruption of the nocturnal melatonin rhythm (88). TCDD has a substantial long bio-half-life (T1/2) (89). This feature makes TCDD difficult to be excreted from the body and it has a long-lasting adverse effect on the organisms. Studies have shown that TCDD can significantly modify melatonin metabolism. It reduces endogenous melatonin levels in rats (90). In fish, TCDD altered the metabolic degradation of melatonin in hepatocytes (91). TCDD exposure lowers urinary excretion of 6-hydroxymelatonin, a major metabolite of melatonin, and accelerates the removal of exogenously administered melatonin from serum. It is speculated that TCDD may enhance the peripheral, i.e., extrahepatic melatonin metabolism. These effects are unrelated to the time of day or to any morphological damage of the pineal gland (92, 93). This melatonin reduction is attributed to its consumption by interaction with free radicals generated by TCDD (94).

The overwhelming evidence shows that TCDD induces ROS production, leading to cardiotoxicity. In animal (rat) study, TCDD exposure results in reduced body and heart weight, impaired mean oxygen saturation, and decreased mean blood pressure and heart rate; however, melatonin treatment significantly reduced TCDD-induced cardiotoxicity (95). TCDD increases

systolic blood pressure and the contractile response to phenylephrine in the aorta, while melatonin reverses these adverse effects induced by TCDD (95). In addition, TCDD causes renal oxidative damage by increasing MDA production but declining glutathione level and melatonin treatment partially reverses these pathologically renal changes (96).

3.2. Melatonin and Formaldehyde (FA).

FA is a health biohazard and widely exists in the human inhabitant environments including urban atmospheres, household air, around cigarette smoking, and other environmental sources. As a disinfectant and preservative substance, FA is also widely used in industrial and medical situations. Individuals, particularly, those in the industrial and medical settings as well as the vulnerable children, are easily to be exposed to and affected by FA (97). Those exposed to occupational FA often suffer from a variety of adverse effects, including depression, anxiety, sleep disorders, and even cognitive abnormalities (98). Occupational FA exposure reduces systemic glutathione levels and brain melatonin concentrations and causes profound oxidative stress. Melatonin administration significantly attenuates FA-induced hippocampal neuronal death, restores brain melatonin levels and slows the memory decline. Based on the animal study, it is suggested that supplementation of melatonin will relieve mental disorders resulting from occupational FA exposure (98). Indeed; melatonin has shown a protective effect against FA-induced neurotoxicity in the prefrontal cortex of rats (99).

Epidemiological and experimental studies have shown a positive correlation between exposure to FA and allergic asthma. FA exposure aggravates allergic asthma symptoms by promoting oxidative stress and activating NF-κB light chain-enhancer in activated B cells and all of these alterations are inhibited by melatonin administration (100). FA exposure also has an adverse effect on the neuronal system in asthma patients. It not only exacerbates allergic asthma-like symptoms but also enhances neuroinflammation. The molecular mechanism is that FA triggers oxidative stress and NF-κB activation in the prefrontal cortex in a mouse asthma model and to stimulate the proinflammatory cytokines, IL-1β, IL-17 and nerve growth factor (NGF) productions. This proinflammatory pathway is blocked by melatonin (101). Moreover, melatonin treatment also prevents oxidative damage and apoptosis of testes in FA-treated rat (102).

3.3. Melatonin and Cyanide.

Cyanide is a highly toxic environmental pollutant that is released into the environment through industrial activities such as mining, electrochemical and chemical pursuits (103). Cyanide anions are inhibitors of cytochrome c oxidase in the electron transport chain and it causes multisystem damages. As a small molecule, cyanide has the capacity across the blood-brain barrier and enters mitochondria of neurons where it binds to cytochrome c oxidase to blocks the electron transportation in mitochondria and results in the electron leakage from the electron transport chain. The leaked electrons interact with oxygen or nitrogen compounds to the ROS and RNS, therefore, triggering the oxidative stress in neurons and glia. Melatonin is present in mitochondria as a mitochondrial targeted antioxidant (104) and it exerts a direct free radical-scavenging activity and also stimulates the activity of mitochondrial antioxidant enzymes to reduce mitochondrial electron leakage, and inhibit the adverse effects of cyanide to protect central never system (1, 105-107). The 6-hydroxymelatonin, a major metabolite of melatonin, also significantly reduces potassium cyanide (KCN)-induced superoxide anion production and LPO content and exerts the similar

neuroprotective effects against KCN-induced neurotoxicity in rat brain tissue as does melatonin (108). As the electron transport chain blocker cyanide significantly suppresses ATP synthesis of mitochondria while melatonin counteracts this suppression and maintains the normal function of mitochondria. This function of melatonin is validated as its antiaging and neuroprotective properties (109). In mice, KCN injection cause severe tonic seizures in a dose-dependent manner. when melatonin is cotreated with KCN, this cotreatment inhibits free radical formation and LPO production and prevents neuron death and lowers the frequency of seizures induced by KCN (110, 111). At the molecular level, cyanide promotes hydroxyl radical generation which can break the DNA double bond and lead to DNA oxidative damage, as the best hydroxyl radical detoxifier, melatonin prevents DNA damage caused by cyanide with high efficiency (112). All the evidence indicates that melatonin may be a promising molecule for cyanide poisoning.

3.4. Melatonin and Polychlorinated Biphenyls (PCBs).

PCBs are the persistently environmental pollutants. Like other pollutants, PCBs also cause oxidative stress in organisms (113). Aroclor 1254 is a mixture of PCBs and it can initiate a spectrum of biochemical and neurotoxic responses in humans and animals (114). Over the last decade, the scientists have conducted a series of studies to investigate the potentially adverse effects of PCBs on central nerve system. It is found that PCBs induces brain tissue oxidative stress and alters activities of membrane-bound ATPase (115) and creatine kinase (116) and finally causes neuronal damage (117). Melatonin treatment alleviates all of these damages via its antioxidant activity. PCBs-induced neuronal apoptosis is also prevented by melatonin (113). Based on these observations, melatonin is tested for the animal model of cerebral cortical neurodegeneration associated with PCBs exposure. The results show that melatonin administration significantly improves motor coordination, reduces anxiety behavior, and also prevents other adverse effects caused by the polychlorinated compounds (118). The potential pathway of PCBs-induced neurodegeneration is mediated by the overactivation of the N-methyl-D-aspartate receptor (NMDAR) followed by activation of voltage-dependent calcium channels to increase intracellular Ca^{2+}. The high concentration of intracellular Ca^{2+} stimulates calpain release which, then, inhibits brain-derived neurotrophic factor and leads to neurodegeneration. Melatonin directly scavenges ROS generated by PCBs and effectively downregulates expression of NMDAR, thereby, it protects neurons from PCBs-induced degeneration (114).

4. PROTECTIVE ROLES OF MELATONIN ON PLANTS AGAINST ENVIRONMENTAL POLLUTANTS

Melatonin in plants is a rapidly developing area in melatonin research, especially the protective effects of melatonin on plants which are exposed to the environmental pollutants. There are many extensive reviews on this subject (119). Since the main topic of this review is focus on animals, here we only give a simple introduction to this issue. Plants similar to animals both are inevitably exposed to the environmental pollutants including the metal or non-metal toxins. Different from animals, the plants face more serious threatening for their survival than that of animals under the environmental pollutants since they have limited mobility to avoid the contaminated sites. As a result, the plants have evolved the specific mechanisms to response to the environmental insults. Melatonin is one of the most effective mechanisms for this purpose. Plants equipment all machinery for melatonin synthesis, particularly in the chloroplasts and mitochondria (120) and

they have much higher melatonin levels than that in the animal circulation. This high melatonin effectively protects of plants against the environmental pollutants. This is manifested by the observation that Cd pollution causes the destruction of the physical chloroplast structure and the physical barrier of plants while these alterations then lead to a compensatory rise in melatonin synthesis and increase the tolerance of plants to the Cd (121, 122). This protective effect is attributed again to the antioxidant capacity of melatonin (123) as well as its ability to reduce Cd accumulation in plants (31, 124). Many studies have documented the protective effects of melatonin on the polluted metal-induced damages in different plants. These include Cd (125, 126), Lead (127-129). Interestingly, the melatonin metabolite of 2-hydroxymelatonin also effectively protects plants from the Cd induced damage with its antioxidant activity and other mechanisms (130). It is expected that the researches related to the melatonin's protective effects on plants against the environmental abiotic stressors will be exponentially increased in the future.

5. PERSPECTIVES

Melatonin is a pleiotropic molecule naturally occurring in all organisms including bacteria, plants and animals. It is the first line defense for organisms to against the environmental insults including the metal and non-metal pollutants. The elucidated mechanisms for its beneficial effects on these pollutants are associated with its antioxidant activity, antiapoptotic process, mitochondrial protection and inhibition of the toxin accumulation. The other mechanisms remain to be clarified. However, the new mechanisms of melatonin's beneficial effects on organisms are continuously emerged. These include melatonin's activities on exosome regulation (131), promotion of ubiquitination (132), histone modification (55), DNA methylation (133), mesenchymal stem cells (134), cancer stem cells (135) and regulatory T cells (136). Whether these newly identified mechanisms of melatonin involving in the reduction of the toxicities of environmental pollutants remains unproven. Thus, further studies are warranted. Based on the evidence mentioned above we can make an assumption that a long-term melatonin administration may be useful in high-risk populations to reduce damage from environmental toxins; especially for those who are experienced the low dose-long term exposure. Melatonin is proven to have the strong protective effects on this type of metal or non-metal toxin exposure. Thus, this assumption should be seriously considered in the further clinical investigations.

6. CONCLUDING REMARKS

The environmental pollutants including metal and non-metal toxins are widely present in the inhabitant environments. They will inevitably cause serious health issues to individuals who are exposed to, especially, the occupational workers. Metal or non-metal pollutants are highly toxic because they interact with biological macromolecules, reduce glutathione activity, and produce free radicals, in turn, leading to extensive oxidative stress which compromises cell function. However, melatonin exhibits profound protective effects on these toxins-induced damages in animals and also in plants (Table 1).

Melatonin, a naturally occurring antioxidant, directly scavenges ROS and RNS or upregulates expressions of many antioxidant enzymes to indirectly reduces these reactive species, therefore, it suppresses the oxidative stress induced by the metal or non-metal toxins to exert its protective effects on animals or plants. Melatonin is also an environmental-friendly substance with low or none toxicity to animals or plants. It is a promising molecule which can be used to detoxify the

environmental pollutants. For this purpose, the further studies are warranted.

Table 1. Summary of metal and non-metal toxicities and the protective effects of melatonin on them.

Toxins	Effects	Mechanisms	Roles of melatonin
Metals	/	/	/
Cd	Hepatotoxicity (19, 26)	Oxidative damage and inflammation.	Inhibition of the TXNIP-NLRP3 inflammasome pathway.
	Neurotoxicity (20)	Abnormal mitochondrial dynamics.	Blocking mitochondrial fusion and fission imbalance and enhancing TFEB-mediated autophagy.
	Carcinogenicity (28)	Oxidative and estrogenic effects.	Inhibition of ERα-mediated transcription in both ERE- and AP1-containing promoters.
	Cardiovascular toxicity (29, 30)	Promotion of systemic high blood pressure by enhancing LPO.	Reduction of LPO production.
	Immunotoxicity; Cardiac oxidative damage (22, 24)		Protection of immunotoxicity and cardiac oxidative damage.
	Reproductive toxicity (testicular injury) (23)	/	Protective effects against male reproductive toxicity.
	Destruction of chloroplast (plants) (29, 36)	/	Increases plant Cd tolerance.
Hg	Endocrine toxicity (40)	Inhibition of synthesis of antioxidant and other metabolic enzymes in the thyroid gland.	Inhibition of oxidative stress and endocrine toxicity.
	Cardiovascular toxicity (41)	Oxidative stress and increases left ventricular end-diastolic pressure.	Enhancement of antioxidant defense.
	Nephrotoxicity (42)	/	Upregulation of stress protein expression and tubule recovery.
	Genotoxicity (38)	Genotoxicity by enhancing ROS.	Inhibition of genotoxicity.
	Neurotoxicity (39)	/	Inhibition of neurotoxicity.
Mn	Neurotoxicity (52)	Mn accumulation, oxidative stress, glutathione reduction.	Increase in glutathione level and activation of Nrf2.
	Motor dysfunction (51)	Oxidative stress and dopaminergic neurodegeneration.	Antioxidant activity and preservation of the DA system.
	Mitochondrial dysfunction (46)	Mitochondrial dysfunction.	Inhibition of mitochondrial dysfunction.
Cr	Improved diabetic status in ZDF rats (Cr(III)) (62)	/	Enhancement of plasma Cr content.

	Antidepressant-like effects Cr(III) (54)	/	/
	Carcinogenicity Cr(III) (55, 63)	Production of hydroxyl radicals and 8-OH-dG.	Prevention of membrane changes.
	Cytological damage in liver (Cr(VI) (57)	Cr(VI) promotes cell necrosis/apoptosis.	Preservation of insulin and glucose levels.
	Testicular histological changes Cr(VI) (58)	Germ cell apoptosis.	Maintaining normal spermatogenesis and male fertility.
	Cytotoxicity Cr(VI (56, 59)	/	Increase in vitamin E and C levels, CAT activity, and/or reduction of hydroxyl radical.
Pb	Toxic metal accumulation (65, 73)	Downregulation of expression of metal transporters in metal excretory organs.	Promotion of Pb excretion.
	Neurotoxicity (67)	Apoptosis.	Inhibition of oxidative stress.
	Genotoxicity (68)	/	Antioxidant capacity.
	Gonadal toxicity (75)	Oxidative stress and endocrine disturbance.	Prevention of gonadal toxicity in a dose-dependent manner.
	Nephrotoxicity (69)	Reduction of NO level and induction of oxidative stress.	Reduction of oxidative stress and nephrotoxicity without changing NO content.
	DNA damage (70)	Reduction of blood glutathione levels.	Protection of low-dose, but not high-dose of Pb toxicity.
	Memory defects (71)	/	Inhibition of oxidative stress.
	Motor deficits (67)	Increase in LPO, TBARS levels, reduction of GPx and SOD activity.	Inhibition of oxidative stress.
	Damaged plant cells (72)	/	Inhibition of the translocation of cytochrome c.
As	Genotoxicity (83)	/	Inhibition of As-induced genotoxicity.
	Carcinogenicity (79)	Promotion of ROS and oxidative stress, upregulation of ATF2 and COX-2 expression, induction of bladder cancer.	Downregulation of ATF2 and COX-2 expression.
	Neurotoxicity (85)	Oxidative and nitrosative stress in the central nervous system.	Inhibion of oxidative and nitrosative stress and proinflammatory cytokines.
	Hepatotoxicity (86)	Inhibition of SOD, GPx and CAT activity.	Upregulation of PI3K/AKT pathway to induce Nrf2 expression.
	Nephrotoxicity (80)	Mitochondrial dysfunction, TNFα-mediated cascade of inflammation and cell death, blocking glucose uptake in kidneys.	Promotion of recovery from As-induced nephrotoxicity.
	Testicular damage (81)	Oxidative stress.	Inhibition of LPO and oxidative stress.

	Breast cancer improvement (84, 88)	Apoptosis in the ERα-positive breast cancer cell line MCF-7.	Upregulation of DNA damage-inducible transcript 4 expression, inhibition of the p38/JNK pathway, and enhancement of ATO-induced apoptotic cell death.
	Bladder cancer (79, 89)	Oxidative stress, upregulation of ATF2 and COX-2 expressions promotion of ROS.	Downregulation of ATF2 expression.
Non metal	/	/	/
TCDD	Reduction of melatonin levels (93, 94)	Enhancement of peripheral melatonin metabolism.	/
	Cardiotoxicity (95)	Induction of ROS production.	Reduction of oxidant activity.
	Nephrotoxicity (96)	Increase in systolic blood pressure, aortic contractile response to phenylephrine and MDA in renal tissue.	Reduction of blood pressure, aortic contractile response to phenylephrine and MDA level.
FA	Neurotoxicity (98, 99)	Reduction of systemic glutathione level, melatonin concentrations in the brain, promotion of oxidative stress.	Attenuation of hippocampal neuronal death, restoration of melatonin levels in the brain, and retardation of memory decline.
	Asthma (100)	Promotion of oxidative stress and activates NF-κB.	Inhibition of oxidative stress, pathological airway response, and NF-κB activation.
	Neuroinflammation in asthmatic patients (101)	Increase in IL-1β, IL-17 and NGF levels.	Reduction of IL-1β, IL-17 and NGF levels.
	Testicular damage (102)	Oxidative damage and apoptosis in rat testes.	Inhibition of oxidative damage and apoptosis in rat testes.
Cyanide	Neurotoxicity (105, 107)	Increase in hydroxyl radical and superoxide anion levels.	Reduction of mitochondrial electron leakage, LPO, superoxide anion, promotion of ATP synthesis.
	Epilepsy (109, 110)	Induction of brain neuronal cell death.	Inhibition of free radical and LPO Formation.
	DNA damage (111)	Promotion of hydroxyl radicals.	Prevention of DNA damage.
PCBs	Neuronal damage (113-116)	Oxidative stress, inhibition of membrane-bound ATPase and creatine kinase activities, induction of neuronal apoptosis, activation of NMDAR, voltage-dependent calcium channels, and intracellular Ca(2+) stimulation of calpain.	Antiapoptotic effects, inhibition of ROS and NMDAR expression.

Cd, cadmium; TXNIP, thioredoxin-interacting protein; NLRP3, NOD-like receptor 3; TFEB, transcription factor EB; ERα, estrogen receptor alpha; ERE, estrogen response elements; LPO, lipid peroxidation; Hg, mercury; ROS, reactive oxygen species; Mn, manganese; Nrf2, related factor 2; DA, dopaminergic; Cr, chromium; ZDF, Zucker's diabetic fat; 8-OH-dG, 8-hydroxydeoxyguanosine; IPA, Indole-3-propionic acid; CAT, catalase; Pb, lead; NO, nitric oxide; TBARS, thiobarbituric acid reactive substance; GPx, glutathione peroxidase; SOD, superoxide

dismutase; As, arsenic; ATF2, activating transcription factor 2; COX-2, cyclooxygenase-2; ATO, arsenic trioxide; TNFα, tumor necrosis factor; PCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; MDA, malondialdehyde; FA, formaldehyde; NF-κB, nuclear factor kappa-light chain-enhancer of activated B cells; NGF, nerve growth factor; PCBs, polychlorinated biphenyls; NMDAR, N-methyl-D-aspartate receptor.

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AUTHORSHIP

YY and RJR contributed to conception, revised the manuscript. ZX and XZ drafted and edited the manuscript. WH, MH, TJ and SJ participated in the reference collection, topic discussion and editing of the manuscript. DXT edited the manuscript critically.

CONFLICT INTERESTS

The authors claim no conflict interests.

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