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Review Article

An Overview of the Mechanisms of Cadmium-Induced Toxicity in the Male Reproductive System

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Abstract

Cadmium (Cd) is a toxic heavy metal that is known to accumulate in various organs and tissues in the body, including the testes. Exposure to Cd has been shown to cause significant testicular damage, including impaired spermatogenesis and decreased fertility in both humans and animals. This damage is thought to be due to Cd-induced oxidative stress and inflammation, which can lead to cellular damage and apoptosis. Cd has also been shown to disrupt the blood-testis barrier, leading to increased permeability and an altered testicular microenvironment. In addition, Cd exposure has been linked to changes in hormone levels, including decreased testosterone production and altered gonadotropin secretion. Reactive oxygen species (ROS) and an imbalance in the activity of antioxidant enzymes cause oxidative stress. The nuclear factor kappa-B (NF-κB) signaling system, which controls multiple genes involved in inflammatory responses including tumor necrosis factor (TNF-α), is activated by oxidative stress. These effects can contribute to decreased sperm count, motility, and viability. Efforts to reduce exposure to Cd may help to prevent or mitigate the harmful effects on testicular function. This can be achieved through occupational and environmental regulations, as well as public education and awareness programs. In this review, we highlight many of the principal mechanisms included in testicular damage. These pathways could be considered promising targets for the development of potential therapies for a variety of important human diseases.

Introduction

In addition to being harmful to humans, animals, and plants even at low doses, Cd (Cd) is regarded as a xenobiotic metal because it serves no vital biological use.[1] In the natural environment, Cd is a heavy metal contaminant that has the potential to be harmful. Living things, water, air, and soil, can be concentrated, accumulated, and magnified. The route of exposure influences Cd absorption, with inhalation contributing up to 50%, ingestion generating an estimated 10%, and skin contact contributing almost nothing.[2] Cd is a common environmental pollutant in many industrial processes and smoking. Cd is a byproduct of the production of other metals such as zinc, lead, or copper, and is mainly used in batteries, pigments, coatings and electroplating, plastic stabilizers, and other applications. Cd enters the food chain after contamination. Humans are exposed to Cd through pollutants in the air, drinking water, and food. Smoking is another source of Cd. After smoking, the Cd content of smokers is 4–5 times higher than that of non-smokers. On average, the daily Cd intake of humans is 1.06 μg/kg body weight. Despite the lower intake of Cd, the elimination half-life of Cd is longer (~20–40 years in humans) and can accumulate in the body. Besides, the testis is the tissue in which Cd can accumulate in large amounts. After 14 days of treatment in rats, the Cd in the testes was 100 times higher than that in the blood. Numerous studies have shown that mammalian testes are sensitive organs against Cd and can cause male reproductive toxicity, including testicular injury.[3]

Cd is a contaminant that is primarily emitted during the production of batteries, electroplating, pigment, plastic, and fertilizer. The overall public is exposed to Cd through toxins in food and drinking water. It was reported that the safe Cd levels are 3 μg/L in drinking water and an annual average of 5 ng/m^3 in air. The preliminary tolerable monthly intake for Cd is 25 μg/kg body weight.[4] However, there are both occupational and non-occupational causes of harmful Cd exposure. The risk factors for occupational

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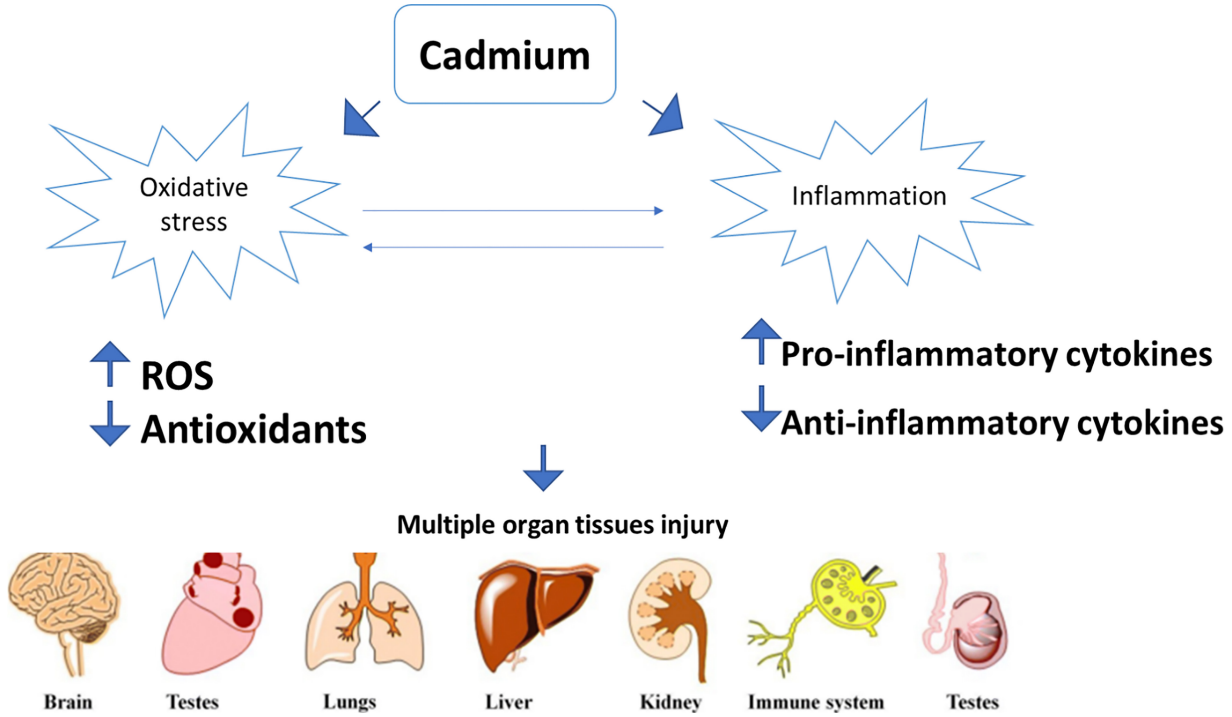

Figure 1. Cd toxicity's effect on multi-organ tissue damage.

exposure include industrial uses of Cd in metal plating, pigments, plastics, glass, fertilizers, and batteries.[5] On the contrary, the main sources of non-occupational Cd exposure are drinking water polluted with Cd, smoking cigarettes, and air pollution. Acute and chronic Cd poisoning has been linked to serious damage and functioning of several body organs, particularly the testes, in both humans and animals (Figure 1). In both humans and animals, acute and chronic Cd toxicity is linked to severe damage to many different organs, especially the liver, and testes. Deposition of Cd causes significant organ impairment in the kidney, bones, liver, lungs, and reproductive organs.[6] Chronic exposure to inorganic Cd causes the metal to build up in many tissues and organs, primarily the liver and kidney, and causes a variety of metabolic and histological diseases.[7] It will have an effect in an increased risk of getting cancer. Despite its industrial importance, recently, it causes cancer in several organs and tissues, the International Agency for Research on Cancer has designated Cd as a Group I human carcinogen.[8] Numerous *in vitro* studies examining the impact of Cd on various cell types exist, and they are based on the wide range of target organs of Cd-induced toxicity.[9-10]

Exposure to Cd and How It Affects Mammals

It is well known that the testis is very vulnerable to Cd toxicity in both animals and humans. Cd toxicity affects a variety of organs, including the kidney, liver, and lungs.[11] Due to its inability to undergo biotransformation and its slow excretion rate, Cd is an extremely hazardous heavy metal. It mostly grows up in the liver and kidneys, where its concentrations are higher than those in the erythrocytes, lungs, pancreas, thyroid, testis, salivary glands, and placenta. It has a prolonged biological half-life, ranging from 15 to 30 years, as a result.[12] In addition, the development of Cd hepatotoxicity occurs in two stages: the first is brought on by direct metal interactions and ischemia, and the second is brought on by inflammation.[13] About half of these individual cases are attributed to male infertility. Exposure to environmental endocrine disruptors has been proposed as one of the accidental causes of male infertility.[14] Natural or synthetic compounds known as endocrine disruptors have the potential to change the endocrine system and have negative effects on people, animals, and wildlife. A very hazardous heavy metal known as cd has been linked to male infertility.[15-17] Cd poisoning in the male reproductive system of humans manifests as male infertility and poor semen quality. Concern over the negative effects of environmental variables is growing as the incidence rate of infertility rises.[18] According to several earlier research, Cd poisoning can result in testicular tissue damage, decreased testicular weights, impaired testicular function, and decreased androgen output.[19] Previous research showed a strong link between Cd exposure and malignancies of the reproductive tissues as well as infertility.[20] Inflammation and oxidative stress are the main contributors to tissue damage brought on by Cd.[21] With the restoration of testicular steroidogenesis, many antioxidants and anti-inflammatory drugs were successful in lessening the damage that Cd caused to several organs, including the testes.[22]

The *in vitro* incubation of human sperms with Cd for a long time (up to 24 h) could significantly decrease sperm motility in a concentration- and time-dependent manner.

The effects of Cd exposure on sperm quality parameters, fertilization capacity, and early embryonic development were investigated. The study showed that *in vitro* incubation of human sperms with Cd for a long time (up to 24 h) could significantly decrease sperm motility in a concentration- and time-dependent manner. Exposure to Cd in the environment for a short term (30 min) did not affect sperm motility but significantly reduced *in vitro* fertilization rate. The effects of Cd at concentrations of 0.62 µg/mL, and 1.25 µg/mL on early embryonic development *in vitro* and observed that the blastocyst formation rate dramatically decreased with increasing Cd concentration. This finding emphasizes the hazardous effects of Cd on sperm quality as well as on natural embryo development and raises greater concerns regarding Cd pollution.[23] The effects of Cd on human fertility have been reviewed in several papers.[24] The association between Cd and male subfertility/infertility is confirmed by epidemiological studies. The relationship between serum heavy metal concentrations and hypoplasia in 50 cases and 50 healthy control boys were examined.[25] Comparing the serum and semen Cd levels of 60 infertile adult males in Nigeria (40 oligospermia and 20 azoospermia) with 40 normal spermia controls, the data have shown that Cd and FSH levels of these infertile patients are significantly higher.[26]

Role of Mitochondria Targeting in Cd-induced Testicular Toxicity

Mitochondria are important organelles that are responsible for energy production, regulation of cell death, and maintenance of cellular homeostasis.[27] Heavy metals are known to have a variety of harmful effects on the body, including the mitochondria which are the energy-producing organelles in our cells.[28] Heavy metals can adversely affect mitochondria through the inhibition of mitochondrial respiration. Heavy metals such as lead, mercury, and Cd can bind to mitochondrial enzymes involved in cellular respiration, leading to a decrease in mitochondrial function and ATP production.[29-30] Increased oxidative stress. Heavy metals can increase the production of ROS in the mitochondria leading to oxidative damage to cellular structures, and impairing mitochondrial function.[31-32] Disruption of mitochondrial membrane potential. Heavy metals can disrupt the mitochondrial membrane potential, which is necessary for proper mitochondrial function and ATP production.[33] Impaired mitochondrial dynamics. Heavy metals can alter the balance between mitochondrial fusion and fission, leading to abnormal mitochondrial morphology and impaired function.[29] These adverse effects of heavy metals on mitochondria can lead to a variety of health problems, including neurodegenerative diseases, cardiovascular disease, and cancer.[34]

Studies have shown that Cd exposure can lead to mitochondrial dysfunction and oxidative stress, which can contribute to the development of testicular toxicity.[35-36] As a result, targeting mitochondria has emerged as a potential strategy for preventing or mitigating the harmful effects of Cd on testicular function. One approach to targeting mitochondria is through the use of mitochondria-targeted antioxidants. These compounds are designed to selectively accumulate within mitochondria and scavenge ROS that are produced during oxidative stress. Studies have shown that treatment with mitochondria-targeted antioxidants can reduce Cd-induced testicular damage and improve sperm quality in animal models.[37] Another approach is to target mitochondria through modulation of mitochondria biogenesis and function. This can be achieved through the use of pharmacological agents or natural compounds that can stimulate mitochondrial biogenesis and enhance mitochondrial function. For example, resveratrol, a polyphenol found in grapes and red wine, has been shown to improve mitochondrial function and reduce Cd-induced testicular damage in animal models.[38] In addition to targeting mitochondria directly, there is also evidence that targeting upstream signaling pathways that regulate mitochondrial function can be effective in reducing Cd-induced testicular toxicity. For example, activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway has been shown to increase the expression of antioxidant and detoxification enzymes, leading to reduced oxidative stress and improved mitochondrial function.[39] In summary, targeting mitochondria is a promising approach for preventing or mitigating the harmful effects of Cd on testicular function. Further research is needed to fully understand the mechanisms underlying Cd-induced testicular toxicity and to develop effective mitochondria-targeted interventions.

Cd Affects Spermatogenesis

Due to the great sensitivity of mammalian testes to Cd, there is a reduction in sperm motility and spermatogenesis index.[40] It has been suggested that prolonged Cd exposure affects the chromatin of the sperm, which is thought to reduce fertility. Testicular toxicity following Cd exposure is typically attributed to oxidative damage along with all of these alterations.[19] Because of this, it is logical to believe that antioxidants may prevent or at the very least mitigate the toxicity of Cd in the testis.[41] The male reproductive system is particularly susceptible to structural and functional abnormalities as a result of prolonged exposure to Cd. N-Acetyl L-Cysteine, quercetin, and curcumin were utilized to reduce and/or stop the harm that Cd-induced damage to the testes produced. Male rats exposed to Cd have also shown a wide range of adverse consequences, including testis necrosis, prostate cancer, damage to Sertoli cells, a decline in sperm quality, and low blood testosterone levels. According to research, Cd's toxic effects on testicular histology are dose-dependent; at 1 mg/kg, the effects were minor, but at 2 mg/kg, there were obvious necrotic alterations. 4 mg/kg was the critical level at which significant necrosis took place. Some rats developed appetite loss and some passed away at doses greater than 4 mg/kg. More studies also revealed that Cd accumulation in semen, even at low levels, may cause oxidative damage and a loss in

sperm quality, which may contribute to male infertility,[42] (Figure 2). A considerable reduction in testicular weights and drop-in androgen production are both signs of compromised testicular endocrine function. Testicular lesions may result from Cd poisoning, according to recent investigations in animals. Additionally, spermatogenic and Leydig cells are degraded by Cd. According to reports, after Cd injection, sperm concentration, testicular and epididymal weight, and the quantity of dead and aberrant sperm all rose. It has been reported that Cd led to necrosis, degeneration, and weight loss of testicular tissues.[43] Additionally, the quantity of undifferentiated spermatogenic cells has a significant impact on the testis' weight. Consequently, the observed decrease in testicular weight, in this case, may be due to Cd's negative effects on the number of germ cells and elongated spermatids. The androgen testosterone, which is released by Leydig cells, is crucial for adult mammalian spermatogenesis. Being an endocrine disruptor, Cd not only controls pituitary and hypothalamic hormone secretion, but it can also interfere with the production of testicular testosterone. Likewise, the drop in testosterone levels may be caused by Cd-induced damage to Leydig cells.[44] Oxidative stress is the main trigger for Cd-induced testicular injury. Consistently, the decrease in serum testosterone caused by Cd administration was accompanied by a large rise in malondialdehyde (MDA) levels in testicular tissues, a considerable reduction in glutathione (GSH) content, and antioxidant enzyme activity of superoxide dismutase (SOD) and catalase (CAT).[45] According to a prior study, Cd significantly reduced the amount of testosterone in plasma and the activity of steroidogenic enzymes in the testes, such as 3 beta-hydroxysteroid dehydrogenase (3-HSD) and 17-HSD. Consequently, the decline in plasma testosterone level brought on by Cd may be directly attributed to the inhibition of the testicular steroidogenic enzyme activities that control testosterone production.[46] The possible connection between this effect and gonadotrophin declines through mediating the transport of cholesterol into mitochondria, steroidogenic acute regulatory (StAR) performs a crucial and restricting role in the production of testicular testosterone. According to a recent study, administering Cd to adult mice significantly decreased the protein expression of testicular StAR, indicating that StAR may be to blame for the Cd-induced decrease in testosterone production.[47]

The testis is extremely sensitive to Cd toxicity. Since the 1950s, studies have shown that *in vivo* acute exposure to Cd caused germ cell loss, testicular edema, hemorrhage, necrosis, and sterility in several mammalian species (e.g., rodents, rabbits, and dogs), and *in vitro,* studies have illustrated Cd-induced damage to testicular cells. Recent studies have also associated reduced male fertility, such as reduced sperm count and poor semen quality, in men exposed to Cd and/or other environmental toxicants. These correlation studies are significant since they illustrate the vulnerability of the testes to Cd toxicity. Sertoli cells (SCs) play a critical role in the assembly of the testis cords during the fetal and neonatal periods.[48] In adult testes, SCs are essential for maintaining spermatogenesis, and the elimination of the SCs in adult testes can lead to the loss of germ cells.[49] Besides, in the fetus, SCs secrete an anti-Müllerian hormone (AMH), which causes the regression of the Müllerian duct. In the fetal life of rodents and humans, the number of SCs increases exponentially, and then slows down after birth and reaches adult levels in early puberty. Cd affects SC development during fetal and neonatal periods.[50] A single intraperitoneal injection of low doses of Cd to rats on GD12 down-regulates the expression of SC genes (*Dhh* and *Fshr*), although this does not affect its number exposure to Cd (1–2 mg/kg, sc) in pregnant and lactating rats can cause vacuolation of SCs and loss of germ cells in the adult seminiferous epithelium. Cd inhibits proliferation and induces apoptosis and DNA damage of immature SCs in the piglet testis. Cd inhibits the interaction between neonatal SC and gonocyte *via* p38 MAPK signaling in the SC-gonocyte co-culture system *in vitro*.[51]

Due to its capacity to interfere with the generation of hormones involved in the control of reproductive processes, Cd is referred to as an endocrine disruptor.[52] It has been extensively used in many industries, including the production of batteries, pigments, plastic stabilizers, electroplating, coating, and alloys. Cd is released into the atmosphere and soil builds up in plants, particularly grains. As a result, consuming food and drinking water, together with inhaling owing to smoking and manufacturing activities, are the usual ways that humans and animals are exposed to such toxicants. Additionally, testicles are thought to be a promising organ for biomonitoring Cd deposition.[53] Numerous investigations showed that Cd may cause significant testicular harm through testicular shrinkage, hemorrhaging, edema, necrosis, and reductions in sperm cell count, sperm motility, and testosterone hormone levels.[54] The main reasons for these effects include Cd's capacity to pass the blood-brain barrier, impact the hypothalamic-pituitary-testicular axis, produce oxidative stress, and release inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-1beta (IL-1β).[55]

The blood-testis barrier is a specialized structure in the testes that separates the developing sperm cells from the blood supply.[56] This barrier is critical for maintaining the proper environment for spermatogenesis, as it prevents toxic substances from reaching the developing sperm cells. Heavy metals such as Cd have been shown to disrupt the blood-testis barrier, leading to reproductive toxicity.[57] Cd can affect the blood-testis barrier through activation of oxidative stress in the testis which can lead to damage to the blood-testis barrier and disruption of its function. Cd exposure can induce an inflammatory response in the testis, which can lead to the breakdown of the blood-testis barrier.[58] The blood-testis barrier is formed by tight junctions between SCs, which are specialized cells that support the developing sperm cells. Cd exposure can alter

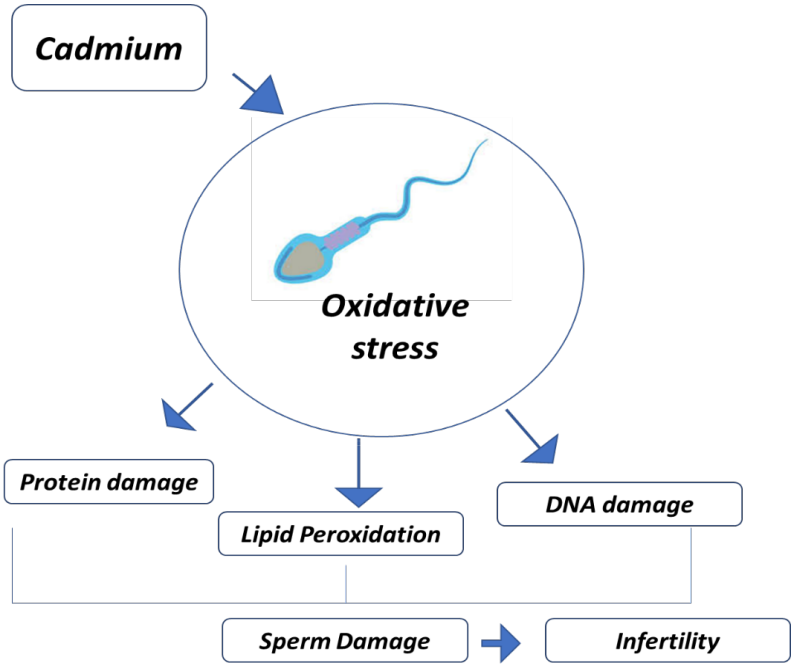

Figure 2. Mechanism of oxidative stress in human semen.

the expression and localization of these tight junction proteins, leading to the disruption of the barrier.[59]

A Connection between Blood Testosterone Levels and Testicular Tumor Necrosis Factor-alpha (TNF-α)

Testicular TNF-α levels are inversely correlated with blood testosterone levels.[60] TNF-α is the "master regulator" of the immunological (inflammatory) response in many organ systems. In other words, Cd led to a large increase in testicular TNF-α and a marked decrease in blood testosterone levels. Macrophages that live in the body and testicular germ cells produce TNF-α. On the Sertoli and Leydig cells of the testes, TNF receptors can be detected.[61] Normally, TNF-α decreased the level of serum testosterone without raising the level of luteinizing hormone (LH) or follicle-stimulating hormone (FSH). The ability of TNF-α to lower testosterone was validated by several in vivo and *in vitro* experimental experiments.[62] Since TNF-α is upregulated in the testis, Cd may be inhibiting testicular function in this instance. On the other hand, the use of fenugreek seed powder (FSP) enhanced antioxidant capacity, increased testicular weight, and restored serum testosterone levels.[63] Daily oral administration of FSP to diabetic rats increased the activities of important steroidogenic enzymes like 3-HSD, 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), malic enzyme, and glucose-6-phosphate dehydrogenase (G6P-DH), as well as cholesterol synthesis in testis, enhancing plasma testosterone levels and sperm count.[64] The polyphenolic components in FSP have also been said to have metal-chelating abilities comparable to EDTA, which adds to the seed's antioxidant capabilities. The production of ROS contributes to the oxidative destruction of macromolecules, which is the mechanism of Cd-induced toxicity.[65] Testicular weight and serum testosterone levels had a negative correlation with the oxidant/antioxidant imbalance in the testes of Cd-treated rats.[66] The depletion of antioxidants caused by Cd was suggested to be one of the causes of increased oxidative stress in the testis. Previous research demonstrated that exposure to Cd caused a severe inflammatory response as seen by increased TNF-α and nitric oxide (NO) expression together with a decrease in Interleukin-4 (IL-4) levels in testicular tissues.[67] This is explained by the fact that TNF-α increases NO production via up-regulating inducible nitric oxide synthase (iNOS). Excess NO causes edema, and cytotoxicity, and mediates cytokine-dependent processes, among other toxicological effects. In addition, superoxide anion and NO combine to generate the peroxynitrite radical, which causes additional cell damage by depleting intracellular GSH and so increasing oxidative stress susceptibility.[68] The hazardous metal Cd targets the testes after acute intoxication and alters the testicular antioxidant defense system, causing oxidative stress to rise. Researchers reported that Testicular GSH, SOD, CAT, zinc, and ascorbic acid decreased may result in an increase in testicular LPO in Cd-intoxicated rats because these antioxidants prevent peroxidation by removing reactive oxygen species. The histopathological changes observed in Cd-treated rats may be brought about by increased oxidative stress.[69]

Anti-TNF-α medications may enhance sperm characteristics and hormone levels in addition to reducing inflammatory illnesses. Anti-TNF-α medications not only reduce inflammatory conditions but also may enhance sperm characteristics and hormone levels.[70] In high TNF-α concentrations, spermatozoa may lose their genomic and functional integrity. TNF-α may therefore contribute to the pathogenesis of testicular injury. In high TNF-α

concentrations, spermatozoa may lose their genomic and functional integrity. TNF-α may therefore contribute to the pathogenesis of testicular injury.[71] The need to look into the potential experimental effects of TNF antagonists in this context is driven by the aforementioned potential roles for these compounds. Etanercept, a biological medication available under the brand names Enbrel and others, is used to treat autoimmune illnesses by inhibiting the inflammatory cytokine TNF-α.[72] The U.S. has permitted it to treat conditions like psoriatic arthritis, juvenile idiopathic arthritis, rheumatoid arthritis, plaque psoriasis, and ankylosing spondylitis. Food and Drug Administration (FDA). An overactive immune system is the root of autoimmune disorders. Etanercept may be used to treat certain conditions by preventing TNF-α.[73] It is a recombinant dimeric fusion protein that binds TNF- and is composed of the Fc portion of human immunoglobulin G1 linked to the extracellular ligand-binding region of the 75-kDa human TNF receptor (IgG1).[74] Etanercept is an anti-inflammatory drug used to treat a variety of inflammatory diseases, including psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis.[75] Spermatozoa can lose their genomic and functional integrity when exposed to high amounts of TNF-α.[70] TNF-α may therefore contribute to the pathogenesis of testicular injury.[76] In a model of testicular damage, etanercept treatment stimulates an anti-inflammatory and antioxidant response.[77] The desire to investigate the potential experimental effects of TNF-α antagonists is driven by the aforementioned potential roles for these compounds. Human immunoglobulin G1 (IgG1Fc)'s region is joined to the extracellular ligand-binding region of the 75-kDa TNF receptor to create the synthetic, dimeric fusion protein known as etanercept, which interacts with TNF-α. By lowering TNF-α, it has the potential to treat several illnesses.[74] In a model of testicular damage, etanercept treatment stimulates an anti-inflammatory and antioxidant response.[77] Etanercept therapy restored testicular weight in a dose-dependent fashion. Infliximab (anti-TNF-α) therapy significantly reduced weight loss in the reproductive organs brought on by Cd exposure. Low levels of TNF-α were crucial in lowering the number of germ cells and elongated spermatids.[78] Etanercept's effect on the increase in testicular weight could therefore be a result of its TNF-α inhibitory properties. Additionally, etanercept therapy lowers Cd levels. According to studies, the induction of Cd caused histopathological abnormalities, affected the composition of lipids, and caused macrophages to release TNF- α, which increased oxidative stress in the organs. Moreover, there is a clear correlation between the levels of TNF- α protein and the concentration of Cd.[79] Testicular oxidative stress was decreased by etanercept administration as demonstrated by lowered MDA levels and increased CAT, GSH, and SOD activity. Etanercept may have a protective effect against cardiac ischemia/reperfusion injury in rats, as demonstrated in a prior study, because of its capacity to decrease lipid peroxidation and improve anti-oxidant enzyme activity.[80] Etanercept prevented NF-κB and iNOS from being expressed while also decreasing the testicular TNF-α level in a dose-dependent manner.[80-81] Testicular activities have been demonstrated to be impaired by TNF-α, specifically steroidogenic enzymes genes expression and steroidogenesis in Leydig cells.[82-83] Etanercept also prevents proinflammatory cytokines like TNF-α from activating the aromatase enzyme, which is "the enzyme that transforms testosterone to estrogen." In testicular tissue, injection of etanercept reduces caspase-3 expression. TNF-α changed the expression of vascular adhesion molecules, which allowed lymphocytes and macrophages to bind to the target site, initiate the inflammation, and induce apoptosis by releasing cytotoxic chemicals. According to studies, etanercept can prevent retinal leakage and cell death in diabetic rats, preserving their retinas.[84] The antioxidant and anti-inflammatory qualities of etanercept may be the cause of its anti-apoptotic effects.[85] Etanercept decreased Beclin1 and LC3B expression. These results could be explained by TNF-α's role in the induction of autophagy.[86] An earlier study found that TNF-α increases hepatocyte apoptosis and autophagy in humans.[87] Therefore, etanercept might prevent the excessive autophagy that Cd exposure causes.

Mechanisms of Cd-mediated Action

Cd-induced cellular injury

Three processes were involved in cellular damage caused by Cd.[16, 88-89] The first deals with interactions between Cd and Ca^{2+}, in which Cd may enter cells through calcium channels and compete with calcium for the binding of calmodulin. As a result, calmodulin and calmodulin-dependent physiological and biochemical processes are disrupted.[90-91] Protein changes are involved in the second process. To create Cd protein complexes, Cd can particularly connect with the hydroxyl, mercapto, and amino groups of proteins. These complexes can block or inactivate many enzyme systems and hurt biological processes. Cd can affect the expression of apoptotic genes in the third mechanism.[88, 92] Cd has the power to modify gene expression and impair DNA repair. The pro-apoptotic Bax gene has higher levels of mRNA expression when exposed to Cd, while the anti-apoptotic Bcl-2 gene has lower levels of mRNA expression. As a result, it causes cells to undergo apoptosis and raises the Bax/Bcl-2 ratio.[93-94]

Cd-Induced oxidative stress

Increased oxidative stress has been linked to cd intoxication.[95] An organ or organism experiences oxidative stress when there is an imbalance in the synthesis of oxidants and antioxidants, favoring the former and leading to cellular disruption. This imbalance may be caused by either an excess of reactive nitrogen species (RNS) and ROS or by weakened oxidant defense mechanisms that remove ROS.[96] However, typical cellular processes like signal transmission, cell proliferation, gene expression, and immunological defense require physiological levels of ROS. The formation and removal of these radicals are

under control by redox balance under normal physiological settings. Nuclear factor erythroid2-related factor2 (Nrf_2) and NF-κB translocation mediate the regulation of redox homeostasis[97], and enzymatic and non-enzymatic antioxidant defenses.[98] The antioxidant system enzymes SOD, CAT, and glutathione peroxidase (GSH-Px) protect against ROS. CAT and GSH-Px purify the hydrogen peroxide that SOD activity generates.[98-99] Contrarily, peroxidases (Px) may work to shield the cell from severe oxidative stress. GSH is oxidized by GSH-Px to glutathione disulfide (GSSG) using H_2O_2.[100] The antioxidant defense system's enzymes adjust their activity to neutralize oxidative stimuli when the cells are under oxidative stress. When the concentration of ROS exceeds the threshold where it cannot be controlled by an antioxidant, oxidative damage to various biomolecules (proteins, lipids, and DNA) may result in cytotoxicity and genotoxicity.[101]

There is growing evidence that the creation of ROS in the testes is connected to the mechanism through which Cd causes reduced male fertility.[102] The antioxidant system and ROS production both help to keep the level of ROS in control. This breakdown of equilibrium causes oxidative stress, which impairs the growth and operation of somatic cells and sperm or triggers apoptosis. Cd (6.5 mg/kg) five days of exposure to adult rats results in an increase in oxidative stress, including elevated levels of peroxidation and nitric oxide and decreased levels of GSH, CAT, SOD, GSH-Px, and glutathione reductase. This upregulates the expression of the pro-apoptotic proteins BCL-2-associated-X-protein (Bax) and TNF-α and lowers the expression of the anti-apoptotic gene (Bcl_2) in the testis, leading to a decrease in cell proliferation. The number of spermatogonia, SCs, and LCs decline, the diameter of the seminiferous tube grows, the number of sperms drops in motility and count, and T synthesis is suppressed in rats exposed to Cd (1.5 mg/kg) for 13, 25, and 39 days.[103] Adult mice exposed to Cd (1 mg/kg, i.p.) for 5 and 8 weeks had higher levels of lipid peroxidation and lower levels of SOD, CAT, and Px in the testes, which increases sperm abnormalities and lowers sperm count.[104] Rats exposed to Cd (40 mg/L) for 30 days had significantly decreased testis and seminal vesicle weights, serum T levels, sperm count, and motility due to an increase in ROS levels and a decrease in CAT and SOD activities. After 24 h, adult male rats get a single dosage of Cd (2 mg/kg, sc). Vitamin C can diminish the activation of TGF and the phosphorylation of p38, a mitogen-activated protein kinase (MAPK). Rats exposed to Cd exhibit higher amounts of ROS and lower levels of glutathione peroxidase and superoxide dismutase, respectively. The ROS levels, SOD and catalase activity, and GSH levels in rats exposed to Cd (3 mg/kg, sc, once daily) were considerably high. The development of testicular injury and dysfunction brought on by Cd is believed to be largely influenced by oxidative stress and inflammation. The nuclear factor-kappa B (NF-κB) signaling pathway, is crucial for regulating some genes implicated in inflammatory responses, including TNF-α, cyclooxygenase-2 (COX-2), iNOS, and the caspase family of proteases, which eventually ends in cell death, is triggered by oxidative stress. Additionally, heme oxygenase-1 (HO-1) is induced by oxidative stress and inflammation and is a key component of the adaptive mechanisms for cytoprotection against cellular stress. Additionally, earlier research showed that many substances with antioxidant and anti-inflammatory properties were useful in preventing Cd-induced testicular damage (Figure 3).

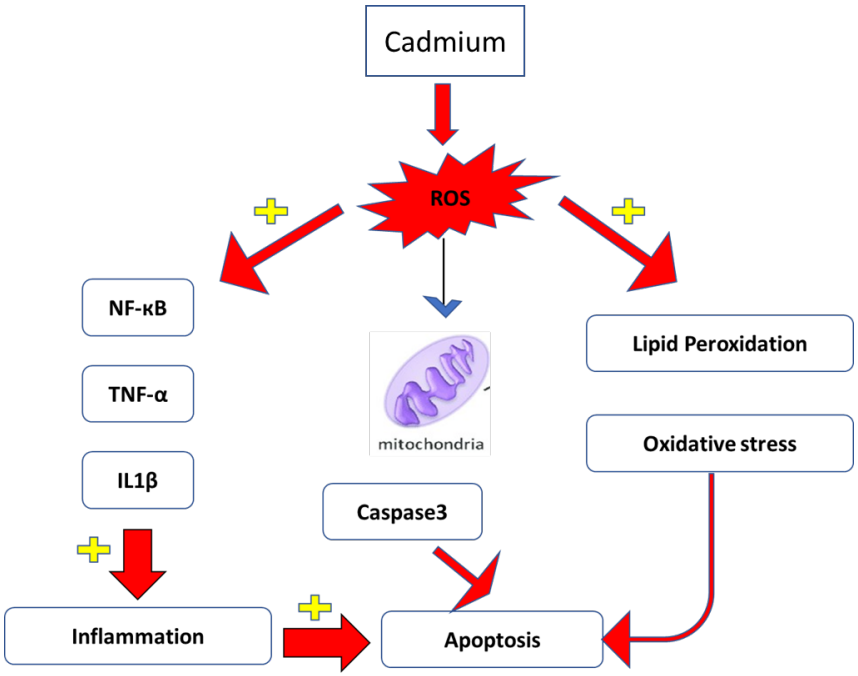

Figure 3. The schematic diagram of Cd-induced oxidative stress.

Cd-induced inflammation

In pathophysiological effects, inflammation and oxidative stress are intimately related and one may be brought on by the other. To eradicate both the initial source of cellular harm and its effects, inflammation is defined as a complex interplay in the vascularized connective tissues in response to exogenous and endogenous stimuli.[105] NF-κB, a key participant in inflammation, is known to be activated by cd-induced ROS due to its redox-sensitivity transactivating several genes implicated in an inflammatory response.[106] The production of pro-inflammatory genes, including cytokines, enzymes, adhesion molecules, and receptors, which are necessary for leukocyte recruitment and cell survival, is controlled by NF-κB.[107] Chemokine synthesis is strongly influenced by NF-κB activation, which also spreads the pro-inflammatory cascade.[108-109] An inflammatory response that has been initiated by harmful stimuli traverses two stages -acute and chronic-each of which is mediated by a distinct cascade. Different manifestations of acute inflammation include an increase in vascular permeability and the recruitment of white blood cells. Cytokines (such as IL-1, TNF-α, IL-6, and IL-8) that increase cytokine cascades and further the recruitment and activation of leucocytes to the site of damage influence acute inflammation.[108, 110] Failure to remove the stimulating chemical from the system effectively causes the acute reaction to transition into a more complex process that results in a chronic response. Monocyte and lymphocyte infiltration, fibroblast proliferation, connective tissue development, and the presence of collagen fibers are all signs of chronic inflammation. IL-12, IL-4, and transforming growth factor-beta (TGF-β) control the activation and differentiation of T cells, which mediates chronic inflammation. The existence of T- and B-lymphocytes may indicate the presence of a persistent stimulating factor. Chronic inflammation causes uncontrolled, ongoing inflammatory cell recruitment that damages tissue by the release of ROS, proteases and nitrogen species by inflammatory cells.[108, 110] Cd exposure changed the redox balance, which caused an excessive amount of ROS to be produced and overpower the antioxidant defenses. Additionally, it induced inducible nitric oxide synthase and cyclooxygenase-2, enhanced lipid peroxidation and arachidonic acid (AA) release, and elevated nitric oxide and prostaglandin E2 (PGE2) production.[111] Through, ROS generation, Cd increased the protein level of TNF-α and IL-6 creating an inflammatory microenvironment,[112-113] (Figure 4).

Cd effect on apoptosis

Apoptosis plays a vital role in controlling the growth and homeostasis of multicellular organisms.[114-115] The two distinct systems that regulate apoptosis are the intrinsic and extrinsic pathways. The B-cell lymphoma 2 (Bcl-2) protein family mediates the intrinsic route, also known as the mitochondrial apoptotic pathway.[116-117] When the Bcl-2/Bcl-2 associated X protein (Bax) ratio falls, cytochrome c is released from mitochondria into the cytoplasm and a caspase cascade is triggered, which leads to the fragmentation of cells. The extrinsic route is initiated when cytokine ligands like Fas ligand (FasL) and TNF link to death receptors like CD95/APO-1 (Fas) and TNF receptors. Caspase-8 is then activated, either directly activating caspase-3 or causing it to merge with the mitochondrial route by cleaving the Bcl-2 family member p22. Caspase-3, which destroys cells, is ultimately activated by both mechanisms. The Fas/FasL system is

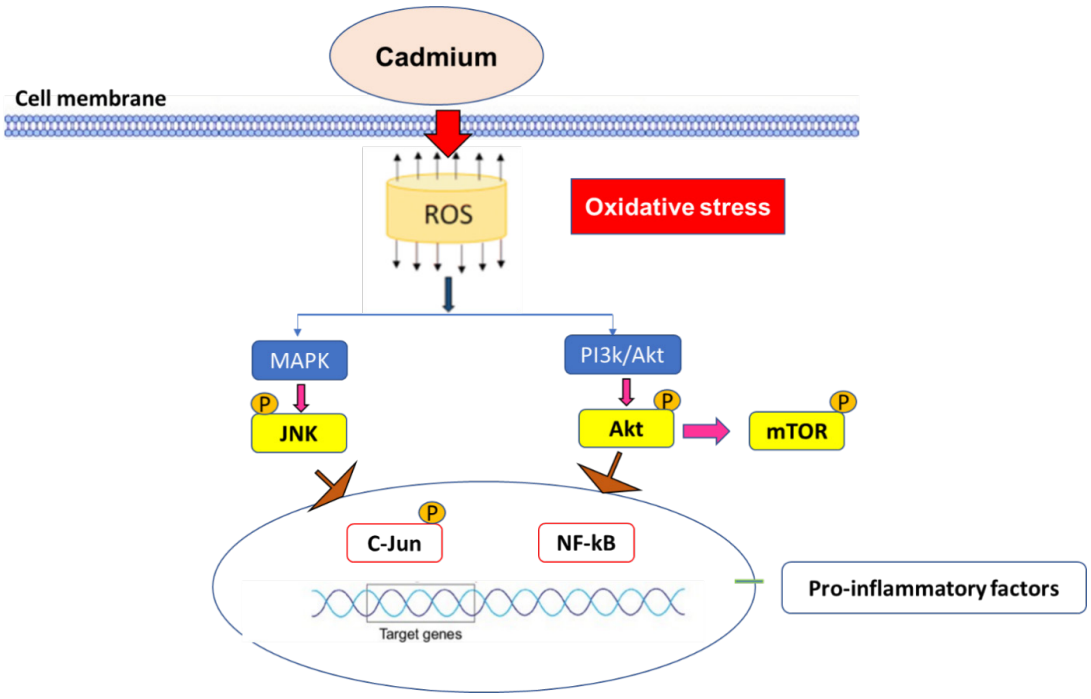

Figure 4. A schematic illustration of the inflammatory mechanism for Cd generation.

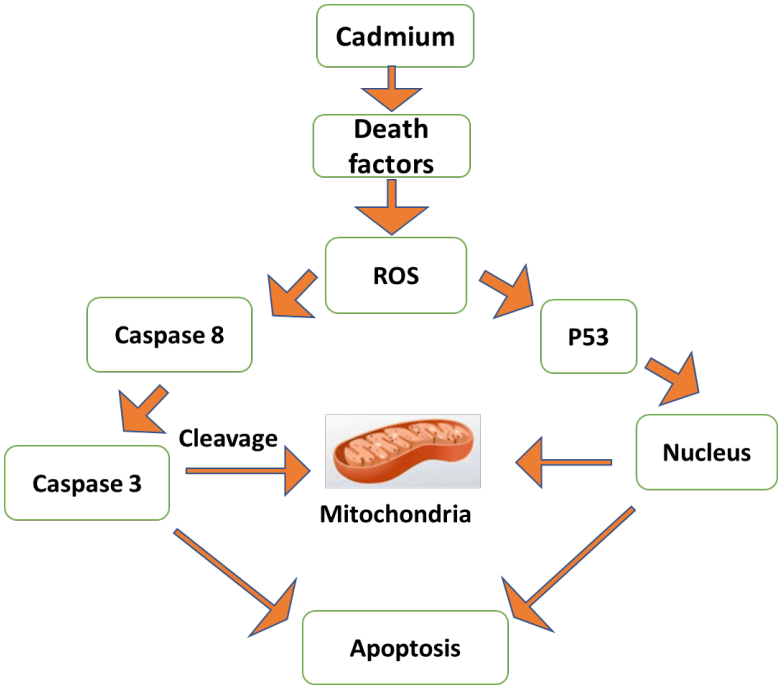

Figure 5. The schematic diagram illustration of mitochondrial-mediated apoptosis induced by Cd.

a key apoptotic route among cell death receptors. The extrinsic route begins with TNF receptors, which belong to the family of death receptors. Fas activation can lead to apoptosis in one of two ways, depending on the kind of cell. Type I cells undergo apoptosis when the effectors caspase-3 and caspase-7 are sufficiently activated by Fas. For Fas-mediated apoptosis to take place in type II cells, the mitochondrial pathway must be involved.

A key part of the Fas-mediated caspase-dependent death pathway, cleaved caspase-8 protein, was produced in greater amounts when Cd was present.[118] In hepatoma cells, exposure to Cd can cause cell death by activating the Fas/FasL pathway. In rat proximal tubular cells, Cd causes activation of the Fas/FasL apoptotic pathway. The number of annexin-V-positive cells and the rate of apoptosis were both elevated by Cd. Cd causes a multitude of death signals to be activated. Numerous environmental factors and genetics may have an impact on the beginning and frequency of death signals. Apoptosis-related mitochondrial membrane depolarization and a DNA damage response start the Cd-induced death process.[119] Renal tubular cells are killed in vivo by Cd. In rats' small intestines, it causes a decrease in the expression of anti-apoptotic Bcl-2 genes and an increase in pro-apoptotic Bax genes. Similar investigations demonstrated that the Bax and Bcl-2 genes were controlled during apoptosis.[120] Both *in vivo* and *in vitro*, oxidative stress damage brought on by Cd can reduce the synthesis of insulin and cause pancreatic islet cells to apoptosis. Similar to this, Through the mitochondria-dependent apoptotic pathway, Cd kills pancreatic cells.[121] In this pathway, increased PARP cleavage, increased caspase-3, caspase-7, and caspase-9 activation are associated with mitochondrial malfunction (loss of MMP, rise in cytochrome c release, drop in Bcl-2, and increase in p53 expression), which is essential for apoptosis (Figure 5).

Cd effect on autophagy

To maintain cellular homeostasis, the catabolic process known as autophagy takes harmful macromolecules, misfolded proteins, and damaged organelles to the lysosome for destruction.[122-123] Autophagy is triggered when cells are exposed to environmental stresses like DNA damage, anoxia, infection, oxidative stress, medication and metal toxicity, and malnutrition. Byproducts of the breakdown of macromolecules like nucleosides and amino acids can be utilized to provide energy for cellular survival. By removing poisonous or damaged materials from cells and keeping the intracellular environment stable, autophagy reduces the accumulation of aberrant proteins and aging organelles.[124] During the autophagic process, misfolded protein substrates are enclosed in a double-layered membrane structure to create autophagic vesicles, which range in size from 400 to 900 nm. The lysosomal membrane and the autophagosome's outer membrane are subsequently combined to form the autolysosome. ROS triggers autophagy by preventing protein kinase B/Mammalian target of rapamycin (AKT/mTOR) signaling.[125] By directly modifying crucial autophagy-related proteins including Autophagy-related 4 cysteine peptidase (Atg4), Autophagy-related 4 cysteine peptidase (Atg5), and Beclin-1 as well as indirectly influencing signaling pathway components like Jun N terminal kinase (JNK) and p38. Autophagy is triggered by minimizing oxidative damage and eliminating toxic cellular components, and this promotes the survival of tumor cells as well as the growth and dissemination of cancer.[126] Previous studies

have shown that autophagy increases tumor survival by suppressing p53. p53 has a variety of effects on autophagy depending on where in the cell it is. Nuclear p53 increases the transcription of sestrin-1/sestrin-2 and damage-regulated autophagy modulator (DRAM), and by activating the mammalian target of rapamycin (mTOR), it additionally prevents autophagy. Transglutaminase 2 (TGase 2)-mediated autophagy causes p53 to be damaged in renal cell carcinoma (RCC) cells, which promotes the growth of tumors. Given that p53 has been linked to Cd-induced kidney damage, autophagy, and p53-mediated apoptosis may be connected. The induction of LC3B-II, mature cathepsin L, autophagosome-lysosome fusion, and activation of lysosomal activity, which is linked to the formation of lysosomal acid, are all mechanisms through which cd induces autophagy. By activating the lysosomal-associated membrane protein and the lysosomal hydrolase cathepsin B, Cd increased the potential for lysosomal breakdown both *in vivo* and *in vitro*.[127] However, Cd inhibits Rab7 protein expression, which increases the fusion of autophagosomes with lysosomes and enhances hepatotoxicity. According to studies, the powerful free radical scavenger puerarin (PU) shields hepatocytes from Cd-induced cell death. A recent study found that PU decreases the production of ROS and malondialdehyde caused by Cd, lowers the hepatotoxicity caused by Cd, and slows cell death. By preventing autophagic flux in AML-12 cells, Cd impairs autophagy and induces an increase in the concentration of autophagosomes,[128] (Figure 6).

Treatment Doses and Time for Cd Administration

The treatment doses and time for Cd toxicity depend on several factors, including the severity of the toxicity, the duration and extent of exposure, and the individual's overall health status.[129] In general, treatment for Cd toxicity involves removing the source of exposure and providing supportive care to address any symptoms or complications. In cases of acute Cd poisoning, immediate medical attention is required, and treatment may involve the administration of chelating agents such as dimercaprol or EDTA to bind and remove the Cd from the body. The specific dose and duration of treatment will depend on the individual's condition and response to therapy. In cases of chronic Cd exposure, treatment may involve reducing or eliminating exposure to the toxin and providing supportive care to manage symptoms and complications.[130] This may include dietary changes to reduce Cd intake, such as avoiding certain foods or using water filtration systems, as well as lifestyle changes to reduce exposure to environmental sources of Cd. Additionally, nutritional supplements such as calcium, zinc, and selenium may be recommended to support the body's detoxification processes and reduce the toxic effects of Cd.[131] It is important to note that there is no specific or standardized treatment protocol for Cd toxicity, and management must be tailored to each individual's unique circumstances. Therefore, anyone who is concerned about possible Cd exposure or toxicity should seek medical advice from a qualified healthcare provider.

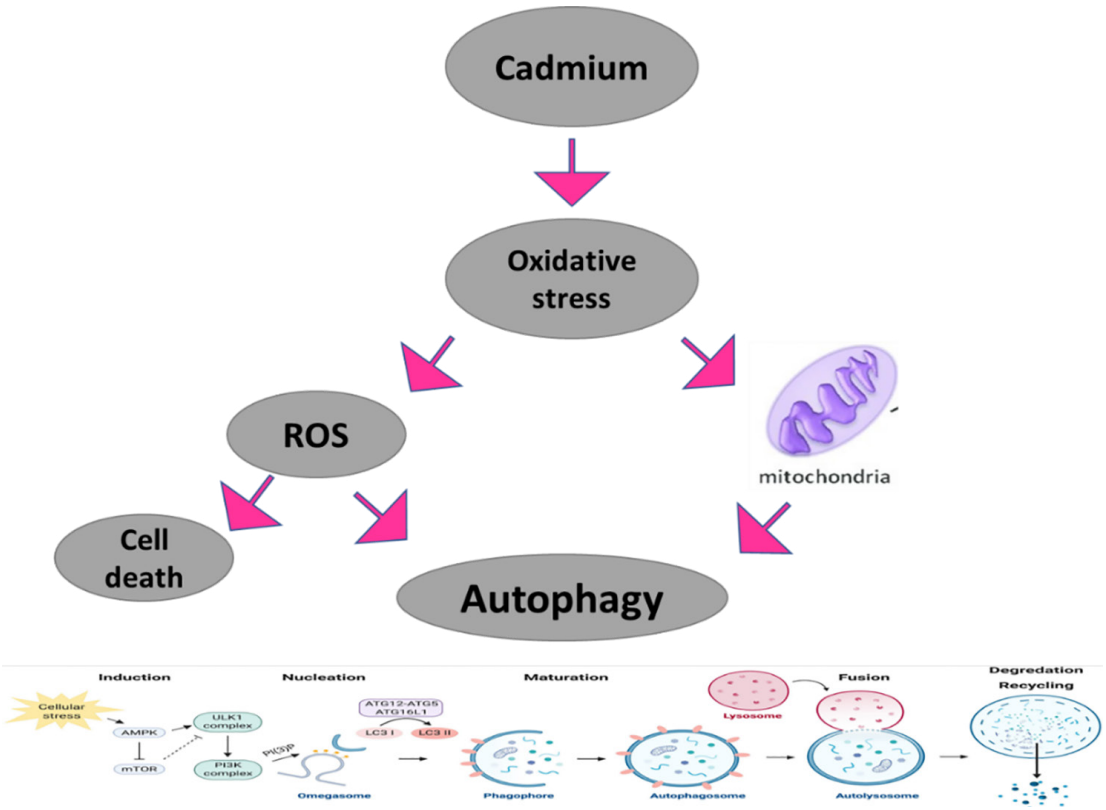

Figure 6. Cd-induced autophagy pathway.

Role of Natural Antioxidant in Reducing Cd Toxicity

Natural antioxidants in our diet may help our body's antioxidant defense system to better defend against oxidative stress brought on by environmental contaminants.[132] Testicles depend heavily on antioxidants with low molecular weight to combat difficulties brought on by oxidative stress since they lack free radical-scavenging enzymes. These substances are generally regarded as free radical scavengers or cleaners.[132-134]

Zinc

A key ingredient in free enzymes like SOD that suppress free radicals is zinc, a powerful antioxidant. This substance acts as a catalyst to move or transfer metals like iron and copper, thereby preventing lipid peroxidation. In one study, testicular tissue lipid peroxidation increased while antioxidant defense capability decreased in rats fed a diet low in zinc.[135]

Vitamins C and E

Strong, lipophilic antioxidants like vitamin E are essential for maintaining and protecting mammalian sperm.[136] This substance has a significant role in the activity of spermatocytes and Sertoli cell lines. Ascorbic acid, a component of vitamin C, is also crucial to the process of spermatogenesis. Hence, a lack of vitamins C and E causes the creation of testicular oxidative stress, which disrupts the process of spermatogenesis and the generation of testosterone. Also, the usage of vitamins C and E can significantly reduce the difficulties brought on by exposure to oxidants including arsenic, Cd, and alcohol as well as testicular oxidative stress.[137] Through inhibiting lipid peroxidation in testicular and mitochondrial microsomes and battling the negative effects of oxidative stress brought on by exposure to substances like ozone gas, iron overload, intense exercise, aflatoxin, cyclophosphamide, and formaldehyde, a study showed that vitamin E was effective on testicular function.

Selenium

Selenium is a crucial mineral for the body's defense against free radicals. This component lessens damage brought on by free radicals and protects crucial antioxidants in the body, such as vitamins C and E. Selenium helps the thyroid gland function by contributing to the synthesis of thyroid hormones. Fertility benefits substantially from selenium.[138] Those with high oxidative stress, such as those with chronic diseases (diabetes, cardiovascular disease, and HIV), elderly persons, alcoholics, and smokers, are advised to eat a selenium-rich meal due to the biologically significant role of selenium, particularly in the male reproductive system. In this regard, a negative relationship between sperm motility and seminal selenium level has been found. Moreover, the semen of fertile men contained substantially more selenium than that of infertile males.[139] Selenium supplementation and vitamin E supplementation significantly reduced malondialdehyde (MDA) and enhanced sperm motility.

Melatonin and cytochrome C

Melatonin differs from other oxidants in two significant ways. First off, melatonin functions as an antioxidant that shares one electron, as opposed to two, in oxidation reactions. Melatonin is hence more vulnerable to destruction from free radicals. Melatonin thus slows down oxidation and the production of free radicals. Second, because melatonin is both water- and fat-soluble, it can easily pass the testicular blood barrier to preserve the germinal epithelium. Melatonin levels in seminal plasma are associated with non-obstructive azoospermia, leukocytopenia, insufficient sperm motility, varicocele, and oxidative stress in the male reproductive system. Melatonin administered intraperitoneally also resulted in a decrease in testicular oxidative stress following the experimental induction of a varicocele on the left side.[140] Cytochrome C is an additional antioxidant that is effective in scavenging free radicals, and it has just been found that it has a special function in reducing testicular H2O2. A little protein called cytochrome C moves similarly to coenzyme Q (ubiquinone). The cytochrome C isoform is known to be a potent apoptosis activator and contributes to enhancing the protective capacity of testicular tissue by eliminating damaged germ cells.[141]

Potential preventive/therapeutic strategies

Several amino acids (AAs) provide significant protective effects in the reproductive system. AAs can counteract xenobiotics-induced oxidative stress.[142] Betaine (tri-methyl-glycine; BET) is an abundant amino acid derivative in daily human food. Spinach, wheat, shrimp, and beetroot are rich sources of BET. Several physiological roles have been identified for BET. Besides its physiological properties, several investigations stressed the ameliorative effects of BET supplementation against oxidative stress and its associated events in different biological systems.[143] Taurine (TAU) is abundantly found in mammalian bodies. TAU as an effective agent against Pb-induced reproductive toxicity. The effects of TAU on oxidative stress markers, mitochondrial function, and the steroidogenesis process seem to play a fundamental role in its protective properties. Further studies are warranted to detect the precise protective effects of this amino acid in the reproductive system.[144]

Conclusion

Cd exposure is particularly concerning in underdeveloped nations, where environmental contamination can lead to liver, lung, and kidney damage and significant disease lesions. Our review highlights the role of Cd in the development of testicular injury, which has become a serious concern due to the contamination of water, air, and industrial sector. In addition, the complex roles of inflammation and oxidative stress in testicular tissue have been discussed. Besides, treatment doses and time for Cd

administration, the role of natural antioxidants in reducing Cd toxicity, and potential preventive/therapeutic strategies were clarified as well.

Author Contributions

Samar A. Antar: Conceptualization, Investigation, Formal Analysis, Writing - Original Draft. Aymen Halouani: Formal Analysis, Writing - Original Draft. Cherry Gad: Writing - Review & Editing. Ahmed A. Al-Karmalawy: Conceptualization, Investigation, Formal Analysis, Supervision, Writing - Review & Editing.

Conflict of Interest

The authors report no conflicts of interest.

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