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Review Article

Cadmium induced toxicity: A Review

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Abstract

Cadmium is a highly toxic metal that can disrupt a number of biological systems. The cadmium is responsible for the generation of reactive oxygen species, glutathione depletion, lipid peroxidation, proteins cross-liking, and DNA damage; ultimately result in oxidant induced cell death. Cadmium stimulates and binds to various biological components such as proteins and non-protein sulfhydryl groups, macromolecules and metallothionein. Cadmium intoxication can lead to kidney, bone, and pulmonary damage, damage to the lungs, liver, and kidneys in animals and humans in cadmium-exposed conditions.This review gives detail about mechanism and diseases of cadmium induced toxicity.

1.Introduction

Cadmium is a naturally occurring element with an oxidation state of +2 [1]. It is chemically similar to zinc. Cadmium primarily present in ores of zinc, copper or lead, and extraction and processing of which releases cadmium into the environment. It is classified as a human carcinogen by the North Carolina national toxicology program. The toxic effects of cadmium on human health were first known in 1858 [2]. Cadmium accumulates and results in toxicity [3].Acute cadmium exposure produced toxicities to the lung, liver, testes, and brain, while chronic exposure to cadmium often leads to renal dysfunction, anemia, osteoporosis, and bone fractures[4].Absorption of cadmium also occurs through skin but it is comparatively insignificant [5]. Cadmium emissions arise from two major source categories, natural sources and man-made (anthropogenic sources). Emissions enter in to the three major compartments of the environment -air, water and soil. Emissions to air are considered faster than that to water, which in turn is considered faster than that to soil. Cigarette smoke is by far the greatest source of cadmium exposure. Cadmium is used in pigments, batteries and reagents [6]. The major source of inhalative cadmium intoxication is cigarette smoke. The human lung resorbs 40–60% of the cadmium in tobacco smoke [7].

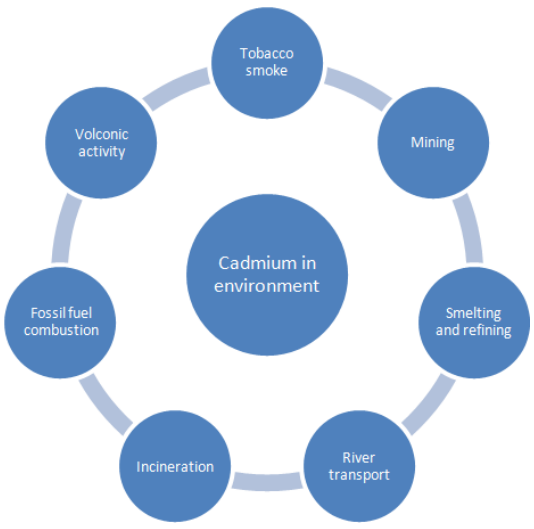

Figure1: Various sources of cadmium pollution in the environment [8]

Cadmium concentrations in healthy persons are less than 1 µg/L in either blood or urine. Persons who have sustained renal damage due to chronic cadmium exposure often have blood or urine cadmium levels in a range of 25-50 µg/L. Cadmium dispersed in the environment can persist in soils and sediments for decades [9]. Cadmium in the dose range 0-40mg/kg while causing a time- and dose-dependent decrease of the basal serum levels of alkaline phosphatases (ALP) also caused a dose-dependent increase in the serum concentration of the acid and prostatic acid phosphatases [10]. The metallothionein play a pivotal role in cadmium disposition after chronic exposure to cadmium [4]. Cadmium inhibits cholinesterase activity in the blood plasma [11]. This depletes superoxide dismutase and glutathione peroxidase antioxidant enzymes [12]. Cadmium exposure can result in loss of smell function. Cadmium changes in DNA structure and altered gene expression, and induction of apoptosis occurs[13].

2. Mechanism of cadmium toxicity

2.1 Plants

Cadmium can induce instability in physiological processes such as photosynthesis, water relations and mineral uptake. The uptake of cadmium by plants may be affected by many variable soils and climatic parameters (ph, genotype).Cadmium is transported through the root cortex to the stele, and from there through the xylem to the shoots, though the phloem is also involved in transportation [14]. Cadmium increases its concentration in crops as a result of long-term application of phosphate fertilizers [2]. Cadmium ions are retained in the roots and only small amounts are transported to the shoots. Cadmium also alters the water relation in plants, causing a physiological drought and causes metabolic dysfunctions [15]. Cadmium stress leads to decreased linolenic acid [16] and protein degradation through amino acid metabolism resulting decreased plant growth [17].

2.2 Organisms

Environmental exposure to cadmium can occur through the diet and drinking water or by cadmium fume inhalation. Cadmium is known to increase oxidative stress by being a catalyst in the formation of reactive oxygen species, increasing lipid peroxidation, and depleting glutathione and protein-bound sulfhydryl groups[18]. Cadmium also can stimulate the production of inflammatory cytokines and down regulates the protective function of nitric oxide formation. Cadmium cannot produce reactive oxygen species directly; the apoptotic effects of cadmium at least in part are mediated via induction of oxidative stress [19]. Cadmium accumulates primarily in the liver. Low molecular

weight protein called metallothionenins in the liver form complex with cadmium (cadmium-metallothionein complexes). Released from the liver into the blood cadmium-metallothionein complexes end up in various tissues and organs of the human body[20].Workers employed in an alkaline battery factory exposed to cadmium-iron dust (5-15 mg/m3 of air) and nickel graphite dust (10- 150 mg/m3 of air) for periods ranging from 9 to 34 years complained of decreased ability to smell,even at low concentrations, cadmium exposure can result in loss of smell function[21]. Cadmium has the capability to bind with cystein, glutamate, histidine and aspartate ligands and can lead to the deficiency of iron. The most important metabolic parameter for cadmium uptake is a person's possible lack of iron. People with low iron supplies showed a 6% higher uptake of cadmium than those with a balanced iron stock.. Low iron blood levels stimulate the expression of DCT-1. It is a metal ion transporter in the GI tract, serving as a gate for cadmium resorption [7]. When cadmium binds to metallothionein protein, its concentration increases by 3000 fold. Zinc present in metallothionein, which acts as antioxidant, which scavenge free radicals, where in cadmium toxicity, zinc is replaced by cadmium, result in cell damage[22].

3. Role of cadmium in diseases

3.1 Carcinogenesis

Cadmium acts as a strong mutagen. Cadmium affects cell proliferation, differentiation, apoptosis and other cellular activities and can cause numerous molecular lesions that would be relevant to carcinogenesis. Cadmium interferes with DNA repair processes and enhances the genotoxicity, result in tumor formation [23].Cadmium induces reactive oxygen species, which in turn increase the probability of mutations and initiate cancer [19].The apoptotic effects of cadmium at least in part are mediated via induction of oxidative stress. A rapid and transient ROS generation by cadmium triggers apoptosis via caspase-dependent pathway and subsequent mitochondrial pathway. CdCl4 treatment significantly increased the levels of apoptotic proteins such as caspases-3, PARP, Bax, Bid and cytochrome C and also increased the levels of inflammatory mediators [1].

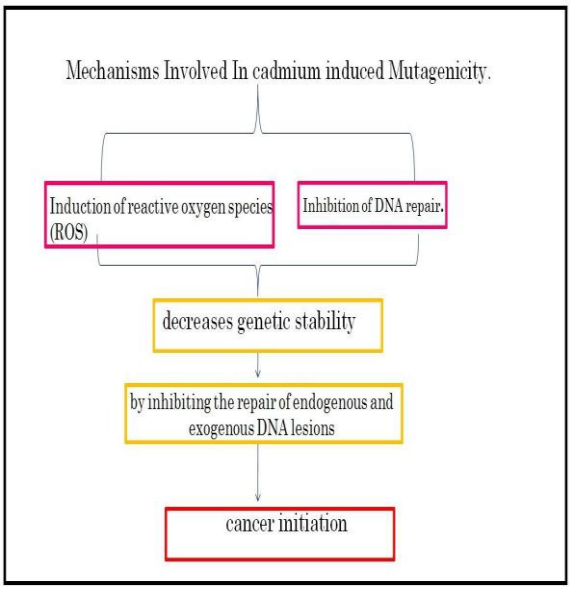

Figure 2: Mechanisms involved in cadmium induced mutagenicity [19].

3.2 Cardiovascular dysfunction

The incidence of cardiovascular disease has increased in the general population, and cardiac damage is indicated as one important cause of mortality. Free radicals may be important contributors to cardiac dysfunction and myocardial damage. Cadmium toxicity induced alterations in heart and muscle tissues of rabbit leading to changes in blood constituents, abnormalities in heart and muscle function altering glycolysis, citric acid cycle, phosphatase metabolism, transamination reactions and induction of free radical stress. The cardiovascular effect of cadmium was associated with regulation of blood pressure. Since both cadmium exposure and the incidence of cardiac damage have increased in recent years. Cadmium-induced peroxidation causes the release of free oxygen radicals [10]. Free radicals might contribute to the alterations processes in heart which result in further injury. Cadmium induced atherosclerosis was reported in rabbit. Zinc-induced protection against the cytotoxicity of cadmium in stellate cells may be related to the maintenance of normal redox balance inside the cell. Thus the free radical induced damage was found to be major mechanism of cadmium induced cardiovascular diseases. Cadmium increases lipid peroxidation and depletes glutathione. Cadmium accumulates in the wall of the aorta. Cadmium is also deposited in vascular smooth muscle cells and produces apoptosis of endothelial cells, results in myocardial structural damage[19].

3.3 Lung damage

The lungs absorb cadmium more efficiently than the gastrointestinal tract. Cadmium reduces the level of antioxidant enzymes activities [24]. Cadmium induced CFTR (Cystic fibrosis transmembrane conductance regulator) dysfunction leads to impaired regulation of the airway surface volume and composition resulting in altered clearance of bacteria and chronic infection and inflammation. Cadmium decreases the abundance of CFTR at the plasma membrane resulting in a decrease in chloride transport in epithelial cells present in the lung. Minute amount of cadmium deposit in lungs if administered intraperitoneal or through contaminating food, it can still induces inflammation and proliferation due to persistent presence in lung cells but these two events may occur independently. The toxic effect of cadmium on lungs was mainly due to CFTR dysfunction, which results in altered bacterial clearance, there by infection and inflammation [19].

3.4 Hepatotoxicity

Acute cadmium exposure may lead to liver damage. Polymorph nuclear neutrophils (PMN) and kupffer cells, contribute to the hepatotoxicity by enhancing inflammatory mediators and promoting necrosis[25]. Activated kupffer cells release mediators such as reactive oxygen species (ROS), nitric oxide, cytokines and chemokines [26] that subsequently enhance the expression of adhesion molecules that leads to inflammation and secondary liver damage. Cadmium produces both dose and time-dependent increases in intracellular glutathione concentration during chronic environmental or occupational exposure at low doses.Cadmium causes a reduction in glutathione content in isolated hepatocytes. Acute toxicity comprises hepatocellular swelling, sinusoidal congestion, pyknosis and karyorrhexis. Cadmium induced hepatotoxicity has been shown to cause early cellular changes in the rough endoplasmic reticulum and nucleus. Later alterations include mitochondrial swelling and the appearance of fibrillar material within the cytoplasm. Liver injury due to acute cadmium exposure is dominated by apoptosis and necrosis [27]. Sub-cellular localization of cadmium demonstrates that cadmium is distributed to the nucleus mitochondria and endoplasmic reticulum, which localizes cadmium in target organelles. Cadmium toxicity causes DNA damage. Cadmium induces significant alterations in the levels of certain enzymatic antioxidant enzymes status in liver [28]. CdCl4 significantly increased the levels of lipid peroxides, oxidized glutathione and decreased the levels of reduced glutathione, SOD (Superoxide dismutase) and CAT (catalase). Production of reactive oxygen species, oxidative tissue damage, apoptosis, glutathione depletion were found to be the major mechanisms attributed for cadmium induced liver injury. When kupffer cells are selectively destroyed, inhibited or suppressed, the hepatotoxicity of cadmium is dramatically reduced [25]. Cadmium inhibits ALP activity [29] and Increase in the levels of ALT and AST. High levels of the alanine transaminase (ALT) and aspartate transaminase (AST) in the liver are also confirmatory of the liver damage. C. sinensis contains many flavanols and polyphenols which probably quenched the ROS produced by cadmium hence showing protection against cadmium toxicity. The protective effect of flavanols and polyphenols present in C. sinensis might be produced indirectly by modifying the enzyme activity thus preventing tissue damage [30].

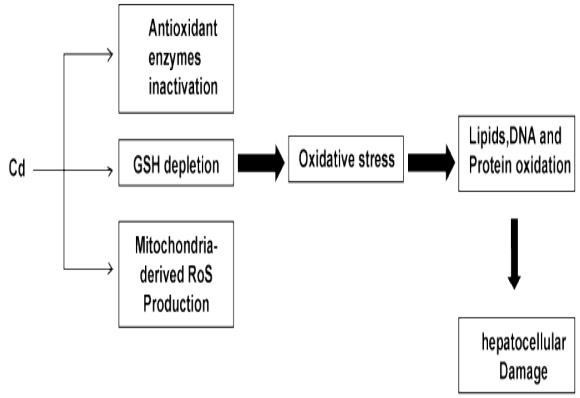

Figure 3: Mechanism involved in Cadmium-induced hepatotoxicity [25].

3.5 Neurotoxicity

Cadmium induces free radicals in the brain and interferes with the antioxidant defense system which in turn leads to cadmium induced alterations of the structural integrity of lipids and secondarily affects the membrane bound enzymes. Cadmium induces the LPO [31]. The brain tissue is highly susceptible to lipid peroxidation (LPO) because of its high rate of oxygen utilization, an abundant supply of polyunsatuated fatty acids, a deficient antioxidant, defense and a high content of transition metals like copper and iron in several regions. The enhanced susceptibility of membranes to LPO can lead to loss of membrane bound ATPase's activities and modulates the cell functions. ATPase's are the membrane bound lipid dependent enzymes, which are involved in active transport, maintenance of cellular homeostasis and also involved in neurotransmission process [32].

3.6 Nephrotoxicity

Cadmium can enter through ingestion, intraperitoneal, subcutaneous, intramuscular and intravenous routes. Chronic exposure of cadmium results in kidney failure and kidney stones [33]. Expression of the ZIP8 metal ion transporter (*Slc39a8* gene) appears to be a key factor contributing to the selective toxicity of cadmium in the endothelial cells of organs such as the testes and kidneys. Cadmium toxicity depends on the level and duration of exposure. Cadmium affects the main tubules of kidney. Humans have a daily intake of cadmium from ingestion and inhalation which is around 20 to 40 µg per day, but only 5 to 10% of this is absorbed. After absorption, cadmium is transported into the blood bound albumin. The cadmium-metallothionein complex is filtered at the glomerulus, but is reabsorbed at the proximal tubule where it remains stored, results in proximal tubular dysfunction by low-molecular-weight proteinuria, glucosuria, aminoaciduria, and phosphaturia [34].Renal dysfunction may be partly dependent upon the biosynthesized amounts of metallothionein in the kidney. Cadmium may cause nephrotoxicity by generating free radicals. On cadmium acetate exposure, the level of urea and creatinine were found to be increased in the serum. Due to the defect in filtration, the level of creatinine and urea gets increased in serum when compared to the normal [35].

3.7 Cadmium –Bone demineralization

Cadmium toxicity decreases bone density compared to the normal decrease in bone mineral density during lactation, and also increases skeletal fragility. Lactation is an important factor contributing to the decrease in bone mineral density safe level for human ingestion is 500µg/week. Cadmium enters in structure of phosphorilation-oxidative enzymes and disrupts producing energy cycles in mitochondria [1]. Environmental exposure to cadmium increases bone resorption in women, suggesting a direct osteotoxic effect with increased calciurea and reactive changes in calciotropic hormones[19].Extreme cases of chronic cadmium toxicity can result in osteomalacia and bone fractures, as characterized by the disease called itai-itai in Japan in the 1950s and 1960s [36].

3.8 Itai-itai disease

Cadmium-polluted rice was the major source of Cadmium intake in the itai-itai disease patients. Calcium is replaced by cadmium result in itai-itai disease. Calcium helps bones to build healthy bones and teeth, keep them strong, send messages through the nervous system, help your blood clot, your muscles contract, and regulate the heart's rhythm, among other things. Calcium transporters have also been involved in Cd transport [37]. Mining or industry's cadmium-polluted waste is released into rivers. This water was then used to irrigate the rice fields. When this is taken up by plants; cadmium concentrates along the food chain and ultimately accumulates in the body of people eating contaminated foods. This disease is found only in Japan[36].

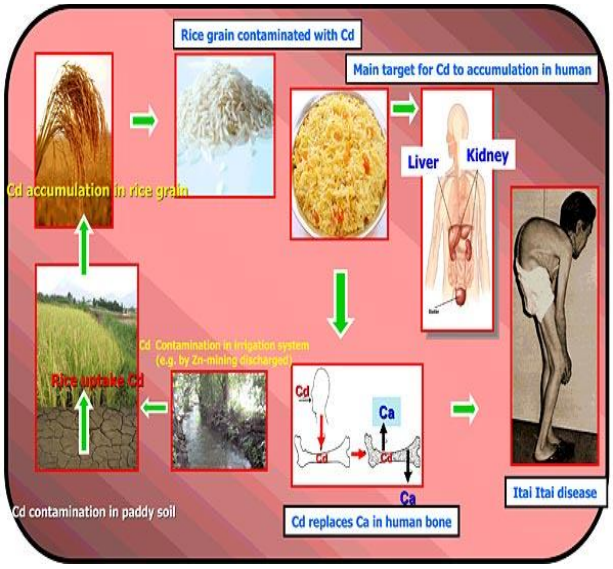

Figure4: Mechanism of itai-itaidisease [38]

4. Conclusion

Cadmium (Cd) is particularly important as it is the 7th highest priority hazardous substance according to the agency for toxic substances and disease registry. Cadmium is an important factor on its gastrointestinal absorption[39]. Cadmium induces oxidative damage in different tissues by enhancing peroxidation of membrane lipids in tissues and altering the antioxidant systems of the cells. Cadmium-induced peroxidation caused the release of free oxygen radicals. These free radicals cause the stimulation and destruction of sensitive macromolecules and indeed tissues [25]. Cadmium alters the water relation in plants, causing a physiological drought and causes metabolic dysfunctions such as production of reactive oxygen species, photosynthesis and nutrient uptake. This decreases the length and dry mass of the plants [15]. The presence of cadmium in the soil decreases the growth of plants. Cadmium is a well characterized teratogens inducing embryo-toxicity, including growth effects, mortality and a range of congenital malformations. Cadmium induces lipid peroxidation, which stimulate oxidative damage in different tissues. This damage to the cell membrane may cause injury to cellular components due to the interaction of metal ions with the cell organelles [18]. As there are no efficient treatment for chronic cadmium poisoning, prevention is the only measure to be taken in order to maintain cadmium level in the environment [9].

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