A Review on the Effects of Cadmium Toxicity on Living Beings

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Cadmium is a toxic transition heavy metal with perilous effects on the health of animals and humans by indefinite ways. It is one of the asserted carcinogens group given by IARC. There are jillion ways by which cadmium may be prevalent in the environment as the pollutant or may be through contaminated water, food or by smoking. Cadmium poisoning may be seen in the form of itai itai disease. It came in knowledge after its outbreak in Japan in 1960s after the consumption of cadmium-contaminated rice as a food source. The exposure and accumulation of cadmium may lead to numerous forms of cancer, including breast, lung, prostate and nasopharynx, pancreas and kidney cancers. It expresses its effect by formation of stress proteins that depends on the amount of exposure and time of exposure. It had shown effects on the functioning of mitochondria resulting in formation of less energy or ATP (adenosine triphosphate) and more ROS. Other effects are cell apoptosis and inhibit growth, division and carcinogenic activity in cells. The current study has been done to understand the various effects scrutinised by numerous workers.

Keywords: Cadmium (Cd); Cadmium dependent carbonic anhydrase (CDCA1); Toxicity, apoptosis; Cancer.
1. INTRODUCTION

1.1 Chemical Properties and source of Cadmium

Cadmium is heavy metals which have no potential physiological function and are considered as a toxic substance in general [1-5]. It is a naturally occurring element in the earth's crust represented by the symbol Cd and with atomic number 48. Cadmium mainly found in the form of ores of zinc, copper or lead and during the extraction process of these ores an enormous quantity of cadmium is released in the atmosphere and soil contamination the human environment. The constant source of cadmium contamination is the use of cadmium in industries as the corrosive reagent, and also used as stabilizing agent in products of poly vinyl chloride, colour pigments, and in the nickel cadmium batteries. Cadmium compounds can tolerate high temperature and can distribute well in various polymeric forms and produces vivid colours with high opacity and good tinting strength [6-11]. They are also known as chalcogenides due to their optical properties which makes them as an integrated part in making of the paintings, enamel, plastic, inks, devices used for displaying, voltaic cell using photons sources, quantum dots [12-18].

Cadmium does not exhibit any vital function in vertebrates, Cadmium dependent carbonic anhydrase (CDCA1) was observed in few of the diatoms of marine water bodies. Cadmium emission arises from mainly two sources;

1. Natural sources
2. Man-made or Anthropogenic source

The environmental sources of cadmium from natural sources are the rocks erosion, land erosion, transport of adulterated soil particles by aerial medium and from and the volcanic eruption. Average concentration of cadmium in the earth crust ranges from 0.1 to 0.5 ppm (parts per million), with mainly accumulate in the sedimentary rocks. High concentration of Cd is also present in the some crustaceans and bivalve, molluscs and crabs and also found in many organisms.

2. METHODOLOGY

Cadmium can be present in soil, water and food. For detecting cadmium there are different ways for different sources. Detection of cadmium from food, water and drink can be done with API's Food Poison Detection Kit and GHM-01 Detector which gives simple and quick result by only change in colour.

Digestion technique for detection of cadmium: There are six digestion techniques for cadmium dry ashing, Acid digestion, microwave digestion, pressure bomb digestion, and extract into IBMK and sulphate ash.

Atomic absorption spectrometry (AAS) and inductively coupled plasma (ICP) are the technique used for detection of heavy metals like cadmium, arsenic, tin and mercury etc. ICP technique are ICP-MS (mass spectrometry) and ICP-OES (optical emission spectrometry). AAS technique include FAAS (flame-AAS), GFAAS (graphite furnace-AAS) and CVAAS (cold vapour-AAS) which are used for detection of different heavy metals. Sample preparation for ICP and AAS can be done by the various ways. Digestion with nitric acid is most common which was confirmed by Roberts and Clark 1986. Technigue used to measure Cadmium in blood and plasma can be done by GFAAS.

The cadmium concentration in biological samples may also be measured by radiochemical neutron activation analysis (RNAA). Cadmium concentration in tissue may be measured by neutron activation analysis (NAA). X-ray fluorescence is also used to detect cadmium amount in the kidney.

2.1 Cadmium Uptake

Uptake of cadmium may take place through contaminated water and food or by the smoking or by atmospheric discharge of the cadmium by mining activity. The fertilizers made from the metal causes sludge formation in the form of sludge on lands used for farming leading to adulteration of land that ultimately enhances uptake of cadmium by the plants grown for consuming purposes. Cadmium and its compound can enter into the body through the respiratory tract as about 30-64% of cadmium has been reported to be inhaled with the cigarette smoke and absorbed by the body. Cigarette contains an average of 1-2µg of cadmium, approximately 0.1-0.2µg of which reaches the smoker's lungs.
2.2 Effects of Cadmium on Mitochondria and Apoptosis

The mitochondria play an important role in maintenance of energy and homeostasis through the process of electron transport chain and produce ATP that is necessary for the existence. Cadmium causes the malfunctioning of the power house of the cell which is in relation to programmed cell death and numerous diseases that even includes cancer.

Cadmium generally targets on the thiol groups (–SH) of cysteine present in the proteins. The sulfhydryl groups of enzymes are the important entities as the dormant state of the sulfhydryl groups in enzymes renders some functions of nucleus, endoplasmic reticulum and mitochondria. Cadmium toxicity is responsible to block the undetermined flow of electron via the IIIrd complex of mitochondrial electron transport chain. Cadmium may change many mitochondrial proteins activity by inhibiting respiratory chain enzymes that hinders the respiration. Cadmium can increase the permeability and can decrease the membrane potential of mitochondria, that activates caspase pathway by releasing cytochrome C. Cadmium can block the activity of various enzymes which indeed can increase the levels of reactive oxygen species (ROS) and peroxidation of lipids. At the principal site of reactive oxygen species (ROS) production inhabit in the complex III, and growth in the amount of reactive oxygen species (ROS) have impacts on the potential of the membrane of mitochondran that initiates various activity including apoptosis (Fig. 1).

There are two main pathways of cell apoptosis:

a) The extrinsic or death receptor-mediated pathway
b) The intrinsic or mitochondrial-mediated pathway

The pathway followed depends on each other and the molecules of the one pathway can influence the other. In extrinsic pathway cell apoptosis occur in the response to the external stimuli, while the intrinsic pathway cell apoptosis occurs in response to internal stimuli, such as DNA damage. There are some toxic stimuli like reactive oxygen species (ROS), UV radiation, ionizing radiation or by the indirectly increases of Ca2+ concentration and ROS (Fig. 1). These stimuli cause the permeabilization of outer membrane of mitochondria that can activate the caspase-8 leading to apoptosis including the clemency of C cytochrome into the cytosol from the intermembranal spaces of mitochondria.

The intrinsic pathway initiated with a fret alarm which itself release by cell like caspase-9 which activates by damage of DNA. In addition of Cadmium toxicity, it also induces the cell apoptosis by caspase-independent events. Excessive ROS production cause the free radical attack on the phospholipids and depolarization of mitochondrial membranes, that makes the prime step of apoptosis of the intrinsic pathway.

In addition of the apoptosis, excessive production of reactive oxygen species which causes the oxidation in macromolecules by the attack of free radical on the phosphate lipids leads in deranging of the integrity of membrane of mitochondria and depolarization, and mitochondrial DNA mutation.

Cadmium can induce apoptosis in the various organs like the liver and kidneys. In cell culture, it causes cellular stress response which is responsible for the mitochondria apoptosis pathway. Cd2+ cause mitochondrial damage which occurs after the fifteen to twenty four hours of exposure to the metal (Fig. 1).

2.3 Relation with Oxidative Stress

The multidirectional toxicity of the metal can cause vital organ failure and devoid the human body into deteriorate form. Cadmium cannot catalyse redox reactions of the bio systems under physiological many proteins leads to variants the potential across mitochondrial membrane. Cadmium exposure increases the production of reactive oxygen species, namely superoxide radicals, hydrogen peroxide, and hydroxyl radical which are generally equitable with the enzyme and non-enzyme barriers. The oxidative stress leads to oxidation as well as impairment of vital macromolecules such as deoxy ribonucletide, lipid, proteins and phospholipids of membrane (Fig. 2).

2.4 Relation of Cadmium and Other Metal Carrying Proteins

Metallothioneins are the proteins with low molecular weight and are of about 7–8 Kilo Daltons in size. They are known by this name because they carry metal ion like Iron, Copper, Cobalt etc. and the protein with high –SH (cysteine) content.
They are very rich in the thiols group. In mammals, there are four different types of Metallothioneins are expressed, which are Metallothioneins1, Metallothioneins2, Metallothioneins3, and Metallothioneins4. Metallothioneins1 and 2 are found in relatively in all tissues where as Metallothioneins3 and 4 are specific in there prevalence in tissues.

The affinity of MTs binding with the ions of metal is metal relying and came out to be the nearby order of Metallothioneins was Cadmium>lead>Copper>mercury>Zinc>silver>Nickle>Cobalt. Generally Metallothioneins binds with Zinc metal and Copper metal, and the attachment relies on the accretion of these metal ions in the renal organ. Cadmium normally accumulates in the liver and kidneys because they can synthesize the Metallothioneins, which act as the precursor for cadmium detoxification. Metallothioneins has high capacity to bind with the heavy metals (like Cadmium), protein also plays a vital role in the fixing of the elements such as Zinc, Copper and Cadmium to control the level and neutralization of the noxious toxins. Metallothioneins works as an imperative agent for protecting against toxicity of metal as well as oxidation reliever. Cadmium forms a complex with Metallothioneins and lead to formation of less toxic substance in other organs. In the kidney filtration the glomeruli reabsorption occurs where cadmium is regained intracellularly. In the last Cadmium is removed from the Metallothioneins and cadmium were flushed into the tubular fluid; and in last it is eliminated in the urine. Cadmium is eliminated by the urine, even if its amount is very less.

Fig. 1. Effects of cadmium on mitochondria and apoptosis

Fig. 2. Relation with oxidative stress
2.5 Carcinogenic Effects of Cadmium

Cadmium was considered as one of the agent having carcinogenic properties as per International Agency for Research on Cancer. The presence of metal in human system reported to induce cancerous activities such as inflammation reactions, oxidation tension, epigenesis, enfeeblement of apoptotic process harming DNA, diminishing recovery rate of DNA, altering gene expression, cell division and abnormal DNA methylation.

The prevalence of Cadmium in place of Zinc in the demethylase of histone can described as the mechanism of Cadmium inhibition of enzymes. In toxicity of cadmium, it requires stress creation by oxidation process which promotes the development of tumor through the mutagenesis. DNA correcting system discards errors of metabolism and environment carcinogenic by using this procedure. The metal cadmium impairs all the repairing mechanism of DNA allowing the aggregation of cells with defected DNA following cell proliferation and mutations.

2.6 Cadmium Effects on the Health

Cadmium is a naturally occurring metal that is used in various chemical forms in industrial processes, and in the pigments production. Environmental exposure can occur by the diet and drinking water. Cadmium is primarily excreted by the urine. Cadmium toxicity leads many hazardous effects on the body. There are two sources of cadmium natural and Anthropogenic source.

Natural sources like rocks erosion, land erosion, transport of adulterated soil particles by aerial medium and from and the volcanic eruption. Anthropogenic sources are cadmium in industries as the corrosive reagent, and also used as stabilizing agent in products of poly vinyl chloride, colour pigments, and in the nickel cadmium batteries. There are many more sources of cadmium toxicity.

Detection of cadmium can be done by the various techniques like atomic absorption spectrometry (AAS), inductively coupled plasma (ICP), radiochemical neutron activation analysis (RNAA), neutron activation analysis (NAA) and X-ray fluorescence. Some simple tests are also available for detection of cadmium which give simple and quick result like API’s Food Poison Detection Kit and GHM-01 Detector.

Cadmium affects the activity of Mitochondria and Apoptosis. Cadmium blocks the activity many enzymes which indeed can increase the levels of reactive oxygen species (ROS) and peroxidation of lipids. There are two main pathways of cell apoptosis the extrinsic or death receptor-mediated pathway and the intrinsic or mitochondriald-mediated pathway. In extrinsic pathway cell apoptosis occur in the response to the external stimuli, while the intrinsic pathway cell apoptosis occurs in response to internal stimuli, such as DNA damage. There are some toxic stimuli like reactive oxygen species (ROS), UV radiation, ionizing radiation or by the indirectly increases of Ca²⁺ concentration and ROS. In addition of it cadmium also induces the cell apoptosis by caspase-independent events. Excessive ROS production cause the free radical attack on the phospholipids and depolarization of mitochondrial membranes, that makes the prime step of apoptosis of the intrinsic pathway.

Cadmium toxicity also causes oxidative stress. The multidirectional toxicity of the metal can cause vital organ failure and devoid the human body into deteriorate form. Cadmium exposure increases the production of superoxide radicals, hydrogen peroxide, and hydroxyl radical which are generally equitable with the enzyme and non-enzyme barriers. The oxidative stress leads to oxidation as well as impairment of vital macromolecules such as deoxy ribonucleotides, lipid, proteins and phospholipids of membrane.

The affinity of Metallothioneins binding with the ions of metal is metal relying and came out to be the nearby order of Metallothioneins was Cadmium>lead>Copper>mercury>Zinc>silver>Nickle>Cobalt. Cadmium normally accumulates in the liver and kidneys because they can synthesize the Metallothioneins, which act as the precursor for cadmium detoxification. Cadmium is removed from the Metallothioneins and cadmium was flushed into the tubular fluid; and in last it is eliminated in the urine. Cadmium is eliminated by the urine, even if its amount is very less.

Cadmium is carcinogenic in humans comes from studies it is concluded that cadmium exposure is associated with lung cancer. Cadmium exposure has also linked to human prostate and renal cancer, although this linkage is weaker than for lung cancer. The presence of metal in human system reported to induce cancerous activities such as inflammation reactions, oxidation tension, epigenesis, enfeeblement of apoptotic
process harming DNA, diminishing recovery rate of DNA, altering gene expression, cell division and abnormal DNA methylation.

3. CONCLUSIONS

The metal cadmium proves to be one of the most toxic elements for human. Human exposure to it may occur through various ways by contaminated food or water or by smoking which lead various harmful effects on human body. It is evidently require dampening the human exposure to the metal and all the aspects of its effect should be studied comprehensively. The ability of cadmium to provoke excessive reactive oxygen species production may force to oxidation in macromolecule, mitochondrian depolarization, and DNA mutation and finally slow apoptosis lowering the mitochondrial membranes potential. So a thorough study is required to check all the aspects of cadmium toxicity at all levels.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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