Biochemistry & Pharmacology: Open Access

Jadoon and Malik, Biochem Pharmacol 2017, 6:3
DOI: 10.4172/2167-0501.1000235

Research Article Open Access

DNA Damage by Heavy Metals in Animals and Human Beings: An Overview

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Received Date: November 25, 2017; **Accepted Date:** December 13, 2017; **Published Date:** December 22, 2017

Abstract

Cancer causing materials are found in air, water and in some other consumer products in the form of heavy metals. Biomedical research has shown that exposure to heavy metals is an important source of DNA damage in human beings and in animals. Heavy metals like iron, copper, chromium, lead, zinc, mercury, nickel etc. and reactive oxygen species enhance peroxidation of lipids and DNA damage. Elements like arsenic, nickel and cadmium are the ambassadors of mutagenic changes in cell. In mammalian cells it was found that DNA single strand breaks chromosomal aberrations occurred and sister chromatids exchange due to various nickel salts. It is now a well-established fact that cadmium causes cancer in tissues of animals. Exposure to cadmium develops cancer in prostate gland, kidney, liver and stomach. Through base pair mutation cancer causing metals damage DNA. However, some heavy metals directly damage the DNA thus generating negative results. The synthesis of nucleic acids and proteins is affected by cadmium. However, cadmium does not have a strong mutagenic nature when compared to other heavy metals. The present review aims to prospect the exposure (of human beings and animals) to heavy metals, cause of different diseases in both and mutagenic effect of heavy metals on double strand repair.

Keywords: Mutation; Mutagenic agents; Apoptosis inhibition; Arsenic DNA damage; Chromatid exchanges

Introduction

In modern world harmful heavy metals are contagious to our health. 65% of North Americans have high quantity of heavy metals in their bodies. Skin disorders, neurological diseases such as Parkinson disease, cardiovascular disorders, carcinoma, tumor, rare autoimmune disorder, degenerative disease are common examples of damage caused by heavy metals [1]. Exogenous and endogenous are two processes involved in damaging DNA. These heavy metals produce reactive oxygen species and bring many changes in the repair mechanism of DNA. These heavy metals have very bad impacts on human health. Depending upon its chemical form, heavy metal (s) cause toxicity or harm the body even if it contains a very small amount of the heavy metal. Different heavy metals in the form of elements cause different diseases in human beings. For example, mercury (Hg) cause lung, heart and kidney diseases. However, some elements like selenium (Se), Iron (Fe), copper (Cu) and zinc (Zn) are very much essential for animals and human beings. The excess and deficiency of these elements cause different problems in a living body [3].

Experimental

Reposition of other minerals within a cell molecule causing DNA damage

The proper mechanism by which heavy metals damage the DNA of the body comprised of heavy metals having greater atomic size within cell molecular structure will replace minerals in the near future. After replacing, the structure of molecule changes which results into two outcomes: Its function may be reduced. As in hemoglobin molecule, mercury is replaced with iron the upcoming molecule will not bind oxygen and hence no oxygen transportation will occur [4]. As the body is up to 70% or more of water a type of battery is created due to two different metals in electrical conducting media and electric current produced results in irregular chemicals harms to the body. This phenomenon usually occurs during dental work. For example metal braces, nickel or gold crown, filled root canals with stainless steel in mouth, it can create up to twenty four per day battery generating electric current which can cause headache, plaguing in blood vessels, bone disorders in teeth, improper heartbeat, less deficient immune system and some other diseases. Body fluids could be created more acidic due to heavy metals. The pH of blood should be constant or it could be fatal to human health. So the reduction in pH value activates the body to make the blood more basic by taking calcium away from bones. The low value of pH results in tumor and osteoporosis in women. Free radical basically means to strip away electrons away from the adjacent molecules. Heavy metals may act as free radical causing damage which includes aging caused by DNA damage, cardiovascular disorders, fatigue and rare autoimmune disorder, arthritis, calcification, chronic arterial rupture and other degenerative problems [5].

Mechanism of DNA damage by certain heavy metals

The genetic material inside the cell is damaged through the interaction between DNA structure and its pattern. Genotoxic substances are the main reason behind this damage of the genetic material. Chromium Cr (V) as transition metal can be mentioned as best example when it reacts with DNA causing serious damage of DNA and leads to toxic diseases. The pentavalent chromium which is very highly stable oxidation state Cr (VI) is achieved through the activation of reduction. Scientists carried out a number of experiments in order

to examine the relationship between DNA and the cancer causing chromium Cr (V) [6]. It is found that the relationship was only specified to the DNA nucleotide (guanine) sequence brings genetic changes. The relationship between the Cr (V) in complex form with the guanine base due to chromium it changes the bases to 8-oxo-Guanine in order to have the oxidation of special site. The damage DNA site changes in to two molecules. After further study these 2 lesions were guanidinohydantoin and spiroiminohydantoin. It is noticed that DNA polymerase was stopped and adenine was include into the DNA opposite site and form the 8-oxo-Guaniosine base. So from this we found that these lesions consist of G-->T transversions. Chromium being high valent acts as cancer causing agent. There is a relationship between DNA and high valent chromium. The exposure of chromate cause DNA damage which leads to toxicity in human beings. It shows Cr (V) plays a role with 8-oxo-Guaniosine producing xenobiotic [7].

Among other harmful substances for genes causing damage to DNA are pyrrolizidine alkaloids (PAs). They were found in some species of plants and they were found to be poisonous for animals as well as for humans; of which the half was found to be genotoxic and most part of it was found to be tumorigenic. After continuous testing and experimentation the scientists made a conclusion that PAs which were metabolically active and cause carcinogenesis diseases. Where DNA breakage, interchange of sister chromatid, micronuclei, variation in genes, changes in gene and changes in chromosome take place. G:C --> T:A is the most common mutation found within genes. It is reported that pyrrolizidine alkaloids are mutagenic *in vivo* and *in vitro*, that's why they are responsible for causing cancer especially in liver [8].

Exposure to heavy metal and its effects on DNA

As we already know that cell consists of proteins and enzymes and there function is to maintain the DNA. External insults and the endogenous processes continuously damage the DNA. These pathways thus become difficult for the survival of cell. One of the cytotoxic damage is the insertion of DNA strand breaks (DSBs) to the DNA helix which causes the death of cell. In the mammalian cells there are two broad classes of DSB repair. One is known as homologous recombination (HR) and the other one is non-homologous end joining (NHEJ). Cancer is caused by damage or the defect of DSBs and also causes unreliability of genome. From environment heavy metals also enter in to body and also damage DNA due to the formation of reactive oxygen species but it also causes alterations in cells. The risk of cancer increases when heavy metals support. The heavy metals which support error-prone repair of DSBs would involve in breeding and brings the changes in DNA. Cadmium, nickel and arsenic are three different heavy metals which were affected include and are repair outcomes of DSB [9].

For the purpose of evaluation our selection of heavy metals is based on three main reasons which are as follows. There is bad impact of heavy metal on human beings. Different heavy metals have different effect and depend on the chemical composition of each heavy metal. A relationship between cancer and exposure to heavy metals has been established and listed their classification as cancer causing agents. Arsenic (Ar+1), cadmium (Cr+7) and nickel (Ni atom no 57) heavy metals are included in the list of carcinogenic elements according to their ranking. The second reason is complex formation and unclear mechanism by which cancer is caused these heavy metals. Some heavy metals are very interesting due to their ability of causing less direct damage to the DNA. For example in bacterial assays, the exposure to the soluble cadmium is not mutagenic or harmful. From such kind of observations we conclude that DNA repair inhibition mechanism works and heavy metal induced mutation [10]. The last reason is based upon the fact that heavy metals selected for the evaluation showed that they stop specific pathways for the individual DNA repair proteins. The different mechanism like nucleotide excision repair (NER), non-homologous end-joining (NHEJ), base excision repairs (BER) and mismatch repair (MMR) is stopped by cadmium. Nickel and cadmium exposure have shown that they change zinc binding domain of XPA (xeroderma pigmentosum group A) which affects its functioning and inhibit performance of NRE [11].

Besides this, cadmium by lowering the amount of nuclear XPC pauses NER response. It also represses ERCC1 expression and diminishes NER response. Arsenic restrains poly (ADP-ribose) and polymerase-1(PARP-1). These substances play vital role in the breakage repair processes of DNA. In human beings, Lymphocytes exposed to arsenic displayed a suppression of ERCC1 (Excision repair cross complementation group l), XPB (xeroderma pigmentosum group B) and XPF (xeroderma pigmentosum group F). By altering the epigenetic regulation of genes, Nickel was shown to change the pathways of DNA repair. For example, in human beings 29 out of 31 DNA repair genes are suppressed by powerful vulnerability of nickel. So, in short, heavy metals have the ability to lower down the capacity of cells to damage DNA. The damaging of DNA by heavy metals and their repair pathways like measuring the concentration of DNA damage by analytical method, variation in chromosome quantity, exchange of sister chromatid detection and measure toxicity are studied with the help of multiple assays [12]. Exposure of heavy metals are evaluated in two methods one method which give an understanding between repair pathways and second method related to information of the repair outcome of exogenously induced double strand breaks. Heavy metal exposure of different concentrations effects on DSB repair mechanism and dominant on cells of mammals. The data related to this tells that exposure to heavy metal directly affects the DSBs repair and repairing of strands [13].

Evaluation of DSB DNA repair pathway: *Ex vivo* green florescent protein (GFP) reporter assay system

The cellular system provides quantitative data on the usage frequency of DNA repair pathways after DSB induction. The system contains four U2OS cell lines (ATCC HTB-96) that consists of single copies of one of four green florescent proteins (GFP)-based reporter cassettes. These four cell lines are:

1. DR-GFP for homology-directed repair (HR)
2. SA-GFP for single strand annealing repair (SSA)
3. EJ5-GFP for total end joining between distal ends of two DSBs
4. EJ2-GFP for alternative non-homologous end joining [14].

A plasmid which expresses rare cutting is involved in the generation of targeted double strand break. Endonuclease performs the function and control the break of DNA strand and their variability [15].

Double strand repair and effect of exposure to heavy metals

There are two possible outcomes of exposure to heavy metals, which are listed below.

1. The cells repaired by the biological pathway stay constant without any process control.

2. The decrease number of repair cells by the pathway analysed shows a preventing effect of heavy metal on the mechanism. Analytical techniques are used to measure the level of DNA breaks caused due to heavy metals. The dose of heavy metals calculated in assay system was unable to give rise to a signal above the background. However this was not a surprising result. The heavy metals like nickel and cadmium are responsible for DSBs. It takes place randomly the genome. There are different methods which are helpful for calculating the effects of heavy metal [16]. Every exposure of heavy metal represents special impacts on the pathways of different DNA repair which are as follows:

Arsenic (As)

The twentieth most abundant element which is found on earth crust is arsenic. It is a semi metal, toxic in nature and cancer causing. It is found in different forms. Mainly in the form of oxide and sulphide, it is also found in salt form with sodium, copper and iron etc. Arsenate and arsenate compounds are the inorganic forms of arsenic and are dangerous to human beings and to their surroundings. Human beings may come in contact with arsenic by several natural sources and industrial ones or from unusual means [17]. Pesticides containing arsenical compounds or unintended disposal of such chemicals and some natural deposits of mineral can contaminate the drinking water. Inappropriate usage of arsenic as in suicidal attempts or accidental children consumption results in toxicity. Arsenic cause's cell respiration malfunctioning and cell mitosis and effect enzyme as it is a protoplasmic poison effecting affecting basically the sulfhydryl group of cells. Inorganic methylated arsenic compounds are transformed biologically into harmful form due to bacteria, fungi, humans and algae to provide mono and dimethyl arsenic acids. This biological process of transformation converts inorganic arsenic species enzymatically into methylated arsenic which shows the severe exposure of arsenic. The methylated end products which are inorganic arsenic compounds formed due to detoxification process known as bio methylation, are excreted during urination indicates severe [18]. Activities of man and natural geological processes results in the occurrence of arsenic contamination. Release of arsenic to the air and soil is due to the melting process both the ancient and new one. The quality of water is affected through such type of sources and ends in water runoff. Arsenic minerals are the causes of ground water contamination by sources of geological importance. Sedimentary and met sedimentary rocks are third type of sources. Higher amounts of arsenic exposure to environment are due to fertilizers and certain pesticides and animal feeding operation. Arsenide and arsenate, the inorganic form of arsenic is considered to be more dangerous to health [19]. These are cancer causing to lungs, liver, skin, bladder and can be referred as highly carcinogenic. Arsenic exposure to humans is by air, food, water and some other factors. Improperly disposed arsenical chemicals and pesticides on all by natural deposit or may by contaminated water. Arsenicosis is the chronic arsenic toxicity. Arsenic toxicity mainly effects skin for example pigmentation and keratosis are the specific skin disorders. Keratosis is also known as "raindrops in a dusty road ". Less exposure to arsenic can lead to nausea; reduce WBCs and RBCs count, irregular heartbeat, needle like sensation in hands and legs and rupture of arteries, veins and blood capillaries. High exposure to arsenic can lead to skin disorders, cancer, brain disorders, cardiovascular disorders and diabetes. The incurable disease caused by arsenic toxicity is the irreversible changes that it causes to the vital organs of human body [20].

Lead (Pb)

Human activities of burning fossil fuel, converting minerals, manufacturing and mining results in deposition of lead and its alternative compounds to environment which include water, air and soil. However we know lead is used for various purposes such as in cosmetic, metal products, batteries and plumbing pipes etc. Toxicity of lead is high so awareness overcome nowadays and reduced its use as in paints and gasoline [21]. The exposure of human being due to lead compounds is mainly due its use in paints, cosmetics, toys, household dusting material, contaminated soil and emissions of industries. Diseases caused in nervous system and gastrointestinal tract shows the signs of accumulation and consumption of high value of lead in children and adults body. Drinking water can also poison due to lead it can be contaminated by water carrying pipes. Lead is considered a carcinogenic compound according to environment protection agency [22]. Chronic effects are caused by lead in different parts of body. Blood flow plays role mainly in distribution of lead to different tissues and more than 90% of lead is accumulated as insoluble phosphate in skeletal bones. Lead poisoning is an another name of lead toxicity which can lead to chronic or acute diseases like loss of appetite, abdominal pain, insomnia, arthritis, renal disorders and fatigue these are causes of acute lead exposure. This kind of exposure is increased due to use of lead in work places and manufacturing industries. If mental retardation occurs or defects during birth and certain allergies occurs, weight loss, hyperactivity, paralysis, weakness in muscle, renal failure and autism are the outcomes of chronic exposure to lead and results in death. Although poisoning to lead can be prevented but it is still a fatal disease which can affect many organs [23]. Edema is caused when lead concentration is elevated from normal level in membranes interstitial spaces of blood-brain barrier (BBB). Intracellular second messenger system is disrupted and functioning of central nervous system is altered due to all this. Main causes of lead exposure are domestic and environmental sources and leads to diseases. We must take precautionary measures to reduce lead toxicity. Lead metal follows ionic mechanism of oxidative stress. This mechanism induces toxicity to human cells. When there is no balance between free radicals and antioxidants that repair the damage cell. Antioxidants protect the cell from free radicals [24]. The lead also decreases the level of antioxidants rapidly. By replacing lead the ionic mechanism is carried out by other cat ions like calcium, magnesium, sodium. The changes that occur due to lead toxicity are apoptosis ionic transportation, enzyme regulation etc. Lead can replace calcium by effecting protein kinase C which is responsible for memory storage and conducts neurological signals. The antioxidant glutathione can be reduced and oxidize simultaneously in the process of reduction glutathione gives (H+) and (e-) to ROS to become stable. In the presence of enzyme the glutathione reduce and binds with other molecule of glutathione by giving end product glutathione disulphide and this happens in the presence of enzyme. This reduce (GSH) form is the 90% of the total content of the antioxidant and the oxidize form of this oxidant is just 10% of it [25].

Mercury (Hg)

The most toxic heavy metal found in the environment is Mercury. The mercury becomes the part of environment by the activity of various industries and pulp preservatives. Mercury Hg in Organic and inorganic form mercury with other elements and cause brain damage and kidney and renal failure. High level of mercury is present in marine food.

Liver of lean fish and certain species of fatty fish being lipophilic in nature are the home sites of higher concentrations of organic mercury. Microorganisms present in soil and water change mercury components into methyl and can be accumulated with increasing trophic levels and with fish age. Mercury compounds are highly carcinogenic and Human nervous system is highly sensitive to all mercury compounds. Brain functions can be altered by accumulation of mercury and causes memory problems and vision or hearing changes can also occur. At high levels metallic mercury vapors even for less time can leads to pulmonary damage, diarrhea, vomiting and skin rashes and cardiovascular diseases. Symptoms to this poisoning include memory problem, hair loss, headache, fatigue these are the common symptoms in other conditions also. According to the world health organization and environmental protection act the mercury standard for drinking water is set at lower levels of 0.002 mg and 0.001 mg [26].

Acute heavy metal poisoning is well known due to mercury exposure. Neurotoxin compound such as methyl mercury is the reason for microtubule destruction and damage of mitochondria within cell and peroxidation of liquid. About 8%-10% of American women have high level of mercury that is responsible for brain disorder in the child they gave birth to. Animals that were exposed to mercury showed changes in behavior for example significant necrosis was observed in rabbits when they were exposed to 28.8 mg of mercury for 13 weeks. Mercury mainly targets the brain. It can even cause damage to nerves kidney and muscle. It can also cause imbalance in calcium hemostasis. The vapors of mercury are dangerous and cause respiratory disorders like asthma. It also causes denaturation of protein structure by affecting its function. It also disturbs the process of transcription and translation by disappearing ribosomes and endoplasmic reticulum [27].

Cadmium (Cd)

Cadmium is the byproduct of zinc production. High level of cadmium is found in rocks, soils and fertilizers. The electroplating of batteries is performed by cadmium. Cadmium is the causes of fair for workers exposed to it as it causes acute and chronic disorders. It is harmful to kidney as it accumulates in the proximal tubule of kidney. Cadmium also cause bone damage for example osteoporosis. It is also mainly responsible for renal stones. Inhalation of cadmium causes lung disorder [28]. Cadmium is highly soluble in water as compared to other heavy metals. Smokers are at the higher risk of cadmium toxicity then non-smokers because tobacco plant can uptake cadmium from the soil and becomes part of cadmium plant. Premature babies arises most commonly n women who are exposed to cadmium during pregnancy. When cadmium binds to cysteine protein such as metalothione its concentration increases by 3000 folds. This protein in the liver causes hepatotoxicity and then moves towards kidney and damage renal tissue and causes nephron toxicity. Cadmium can replace zinc and act as a free radical in spite of it within the cell. Transformation of 16HBE cell is caused due to cadmium because the tail length of untransformed 16 HBE cell of DNA were longer but after treating it with cadmium, this transforms and carcinogenic cell were even longer than the untransformed 16 HBE cell. This is 35 passage transformation of DNA. Cadmium induces apoptosis. Cadmium toxicity involves DNA strand breakage. Multiple mechanisms are involved in cadmium carcinogenesis and DNA repair inhibition occurs. Genomic mutation can be induced by exposure to cadmium and can induce hyper mutability of mismatch repair depression in yeast. Severe cause of instability of genome through mutation has also been studied by accumulation of cadmium [29].

Cancer development may also occur and lead to increase genomic instability. Respiratory system suffers from great harms and toxicity and carcinogenicity in exposure to cadmium. However these effect are not yet well understood but the chronic exposure to cadmium metal can cause damage to gene expression, cell apoptosis, DNA repair capacity.

Alloys, plastics, pigments, nickel cadmium batteries contains cadmium as an important heavy metal. Free radical production is stimulated resulting in deterioration of DNA and proteins and severe pathological conditions. In human and animals, apoptosis and DNA damage due to its sequence abnormalities also occur due to accumulation of cadmium [30].

Cadmium exposure, nickel and arsenic favour repair of DSBS

A different set of embryonic kidney of a stable human was used for analysis. One of the Alu-Alu recombination-Puro (AARP) cassette variants that contain dissimilar anthrobacter lueuts is present in human embryonic kidney (HEK) cell lines. Alu elements which were present in human genome are representative of the variation. There are three AARP variants which contain Alu elements with different percentages (5%, 10% or 15%). Alu1 and Alu2 were tested for sequence divergence. The overall number of Puro AARP colonies observed is rejected because some heavy metals showed no effect and some calculating metal treatments using the diverged AARP cassettes [31].

The exposure effects of heavy metal was checked on repair of DSBs or not, an I-scel expression vector was used to transfect the cells. The cleave between two Alu sequences and resultant exogenous DSBs. This shows the effects of heavy metal (1) On the treatment of DSB repair, (2) The presence of imperfect Alu homeologies. Heavy metal reacted I-scel transfected cells as a result there was no increase in puroR colonies as compared with control. The repaired strands were counted from isolated DNA which are individual puroR colonies in the form of Polymerase chain reaction (PCR) [32]. However, the number of puromycin resistance gene R (puroR) colonies was not very much different from recovery and arranging of a number of individual repaired events witnessed that is repaired happenings altered in the treated cells that are relative proportion of NAR to NHEJ. NAR over non homologous end joining (NHEJ) favoured Alu-mediated treatments of heavy metals (Cd, Ni, As) as compared to control. There may be three possible conclusions:

1. An increase in NAR repairs

2. A decrease in NHEJ

3. Both NAR and NHEJ increase or decrease. These three heavy metals have ability to inhibit any repair protein [33].

The DNA repair pathway depends on 2 things i.e., damage sites of DNA and stages of cell cycle. They observed the effect of heavy metals on cell cycle. Some heavy metals effect on cell cycle. It also depends on exposing condition of metals and also on concentration of heavy metals [34].

Change in sequence of end joining double strand break (EJ DSB) due to nickel and arsenic in the exposure of cadmium

The heavy metal contrast investigation showed the value of repaired DSBs by EJ incidents relative to NAR incidents was decreased. As compared with controlled DNA (without being treated with heavy

metal) showed different sequence characteristic of the EJ repair incidents of DNA. A large number of sequenced break point junctions from the cells which were untreated with EJ repair events displayed micro homology. Relative to this all the treatments of heavy metals decrease in the variety of incidents with micro homology and it happens at the repair site of non-template base insertion. This was a great difference because the insertions were not noticed in the untreated control. The produced chimeric Alu in an inverted orientation showed a recombination in case of nickel treated event [35].

There are many DNA repair pathways which approach each other to repair DSBs. The pathway of DSB repair is categorized into 2 basic groups which are:

1. Sequence homology (HR and SSA) uses for repairing
2. Non-homologous end joining (NHEJ) for involvement of repairing.

DNA DSB repair out comes is effected by exposure of heavy metals. Multiple repair pathways of protein can be stopped by heavy metals. However this depends upon functional requirement of damage protein. The heavy metals have tendency to stop the activity of repair proteins, it also depend on DNA repair and changes outcome of repaired DNA [36], for example, DSBs through alt-NHEJ in the exposure of arsenic. The movement of AKT is suppressed and it inactivates Rad51 (HR) in the exposure of arsenic trioxide. The sequence insertion of DSBs repair sites increase due to heavy metals [37].

Chromium (Cr)

Chromium element on earth is the 7th most abundant and occurs in several oxidative states from (+2) to (+6) in environment. The most abundantly occurring forms of chromium is +4 and +6 is being toxic to plant, humans and animals. This metal occurs naturally by burning coal, petroleum, oxidants of pigments, fertilizers, oil well drilling and metal plating tenures. Fertilizers and sewages are the common sources of release of chromium in environment anthropogenically [38]. Reduce form of chromium is immiscible and insoluble in water. Residue in the organic matter of soil and aquatic environment are sulphates (SO42-) and hydroxides and found to be toxic for human. Extensively industries using chromium (Cr) such as electroplating and wood preservatives, production of paints, pulp and paper etc. Major role is played by these industries by polluting the environment and causing the adverse effects on biological and ecological species with chromium. Agricultural and industrial practices on chromium increase the level of toxicity in surrounding of living beings. Hexavalent chromium being greatest concern in recent decades considered to be most pollution causing in environment. As the environment is in excess with oxygen the kinds of chromium are oxidized to extremely harmful and poisonous and highly soluble in water. Underground water chromium level India has been witness to be higher than 12 mg/L. Metabolic regulation and changes at biochemical level are not exemplified by the mechanism of ultra-structural organization [39]. The toxicity of chromium is not high in aquatic environment because Industries discharge large quantity of chromium in soil and in underground water. Chromate manufacturing process deposits chromium residues and waste water material and water discharge causes serious pollution to farm land.

The industrial discharge of chromium into waste water and waste water irrigation ends up effects the soil also imbalance in the vegetable yield and its quality occurs. Consumption of toxic plant affects the biological factors. Phytotoxicity due to chromium is the common feature in reduction of root growth, inhibition of seeds, germination, suppresses biomass and chlorosis of leaf. Biological processes effect by large chromium toxicity in various plant cauliflower, citrullus and in vegetables. Necrosis and chlorosis are the major abnormalities caused in plant due to toxicity of chromium. Excess supply of chromium catalysis the activity of inducing toxicity has been observed with the process of photosynthesis protein convert in algae, reeducates activity of nitrate (NO3-1) and photosynthesis pigments process of simple diffusion is required to enter into the cell for chromium+3. Some chromium compounds, in contrast to other can easily pass through membrane of cell. Weak membrane permeability of trivalent chromium is harmful on the other hand hexavalent chromium passes through the cell membrane. It is strong oxidizing agent and it is reduced to pentavalent and tetravalent chromium. Chromium6+ is more dangerous than chromium3+ because hexavalent chromium enters the cell rapidly than trivalent chromium. Hexavalent chromium is considered group 1 in cancer causing. The reaction of hexavalent chromium and reduction such as thiol produce reactive oxidant species such as hydrogen peroxide that causes damage to DNA and proteins [39].

Aluminium (Al)

The third most abundant element which is present in earth crust is Aluminium. The main sources of aluminum consumption admittance in human body are by skin contact, inhalation etc. we are exposed to aluminum by water, food and drugs containing aluminum. Symptoms of high level of aluminum in body are vomiting, ulcer, skin rashes, bone pain. These symptoms are for short period of time. Aluminum is purely in the human body. Aluminum exposure can cause Alzheimer disease. It has several effects on brain and can cause loss of memory and imbalance in human posture. Aluminum is hard to eliminate from the kidneys by the patient suffering from kidney diseases as it can lead to bone damage. Dusty environment and kidney disorder and contaminated water are the factors of aluminum toxicity. Most of the cellular and physical processor interchange and interferes with aluminum. The absorption mechanism for aluminum by gastrointestinal track is not yet explained [40]. A proper time period according to literature surveys is difficult to calculate the symptoms of aluminum toxicity are not yet examined. Interactions between aluminum and plasma membrane, Apo plastic and sym plastic targets results due to aluminum accumulation. Al+3 replace Mg+3 in humans causing disturbances with intermolecular and intercellular communication and cell growth end secretary functions. The symptoms observed in Alzheimer patient are same as that evoked due to aluminum in neurons. Complications observed due to aluminum (Al) toxicity or neurotoxicity effect such as atrophy of neural function [41].

Iron (Fe)

Iron is important for growth and survival of human beings. It is the important component of algae and enzymes as well as hemoglobin which is oxygen transporting protein in the important component of algae and an enzyme as well as globulin which is oxygen transporting protein in the blood. Iron undergoes redox reaction. Iron pyrites undergoes oxidation and form sulphuric acid (H2SO4) with ferrous (Fe+2) is about 0.6 nM in deep ocean. While in fresh water it is very low in concentration and is highest in ground water. Many people have

been exposed to iron through drinking water that was collecting from ground. Fishes are affected by iron contamination. They disturb the respiration of fishes. Rice is also effects by iron toxicity. Iron stops rice production and causes zinc deficiency, the rice which are rich in iron are known as low land rice and they uptake Fe+2 by root resulting in loss of yield [42].

When iron fails to bind with protein they form harmful free radical. This harmful free radical which affects the level of iron in human cells, damages digestive track, they also penetrate into cells of liver, brain and heart and mitochondrial. Over intake of iron can increase the risk of these free radicals to cause further DNA damage. Then these free radicals are also responsible for mutations and transformation [43].

Results

Heavy metals damage DNA in human beings

There are total 36 metals out of which 23 are heavy metals: zinc, uranium, tin, vanadium, thallium, tellurium, platinum, silver, nickel, manganese, mercury, lead, gold, iron, copper, gallium, chromium, cobalt, cadmium, serium, arsenic, bismuth, antimony. Environmental and diet are the sources of heavy metals. Their consumption in moderate amount can be required for good health but excessively it can cause toxicity. The toxicity of heavy metals causes damage to brain, heart, lungs, liver, kidney etc. excessive exposure leads to muscular disorders, neurological disorders, Parkinson disease and Alzheimer disease and muscle loss. Even cancer can be causes by repeated excessive exposure [44].

Proof change in DNA and mutagenic effects on mice induced by nickel

The toxic effects induced due to nickel cause oxidative damage. However, oxidative damage due to nickel in the body tissues is well studied. First of all the profile of nickel toxicity was examined and studied in the adult albino mice. Single and multiple sub lethal doses were used in intraperitoneal to study the effect on testicular histoarchitectural, lipid peroxidation (LPO). In testis and epididymal sperm, DNA damage, apoptosis in testis and sperms with damaged head. However, the small amount of dose of nickel induced very small LPO response. Greater doses elicited a normal increase in LPO. Mitochondrial and microsomal fractions increase with high dose of nickel. [45]. This is now a well-known fact that an increase in number of single strand breaks increases the rate of DNA damage. At higher doses, apoptosis was induced by nickel and was examined in testis biochemically. Further analysis for the abnormality of sperm head revealed a nearly 3-4 times increased in the abnormal sperms as compared to the sperms of that were treated by nickel during first 21 days. Going further there are breeding between male and female where males treated with nickel for 35 days and untreated females results in the increase in male-mediated dominant homicidal kind of mutations during the first 21 days. From this we find that toxicity in testis due to nickel compounds can enhance the production of reactive oxygen species. Nickel salts are very hazardous for human health, although many nickel compounds reach in the environment. Nickel has been classified as a cancer causing agent and shows high cancer rate in nasal and lungs in refinery workers [45].

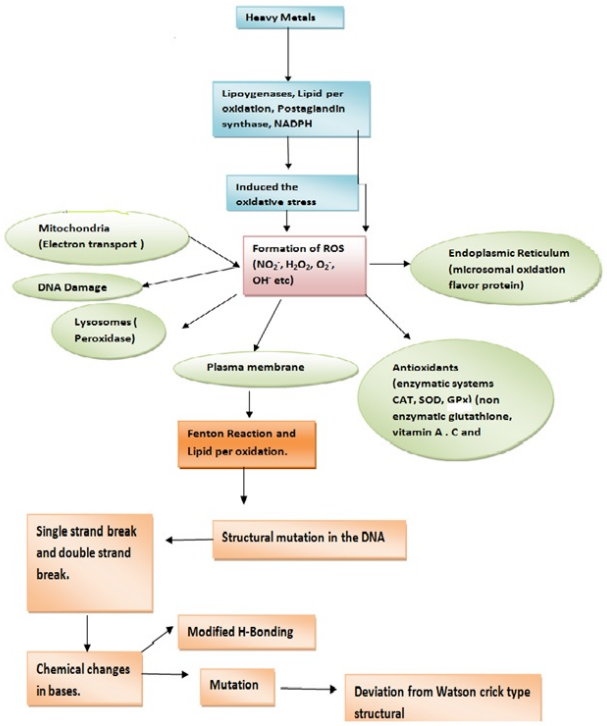

Figure 1: DNA damage due to heavy metals.

Discussion

Explanation of Figure 1 reactive oxygen species are produced due to different heavy metals like Al, Cd, Pb, Cu, Hg and As. The motivating activity of NADPH helps to generate ROS, where Lipoxygenase enzyme catalyzes the hydroperoxidation of unsaturated fatty acids of cell membrane. Nicotinamide adenine dinucleotide phosphate (NADPH) bound with plasma membrane when oxidative stress occurs due to imbalance between antioxidants or accumulation of ROS. When oxidative stress happens, cells attempt to an opposite effect and bring something to redox balance. Higher production of reactive oxygen species induces oxidative stress. Different types of ROS are formed on cell membrane like superoxide (O2-), hydroxyl radical (OH0), hydrogen per oxide (H2O2). The targets of these ROS are lipids, proteins and DNA. First target is the cell membrane in which ROS breaks the lipid chains that enhance the fluidity and permeability of cell membrane. Second target of ROS are proteins. It modifies the amino acids, break the peptide and increase the proteolytic degradradation. ROS not only damage the deoxyribose sugar by removing hydrogen atom but also change the DNA structure in the form of degradation of bases (purine and pyrimidine), break single and double bond. 8-hydroxydeoxyganiosine (8-0H-dG) is produced in this process. Haber Weiss and Fenton reaction also produce ROS and damage protein, carbohydrates and DNA. Lipid peroxidation is a process in which ROS formed by taking electron from poorly unsaturated fatty acids. ROS damage DNA by modifying the bases. Mitochondria produce ROS under normal conditions but under stress conditions produce more. There are two types of antioxidant. Enzymatic antioxidants are superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX), glutathione reductase (GR) and

gualacoal peroxidase (Gpx). The vitamin C, E and glutathione are non-enzymatic antioxidents. The potential biomarker of carcinogenesis is 8-OHG which is best known for DNA damage adducts where ROS disrupt the membrane lipid bilayer due to the process of lipid peroxidation and forms adduct of malondialdehyde (MDA). Isoprostane is indirect biomarker of oxidative stress. ROS produce signal transduction cascades that transmit the information from one side of cell to inside in a cell.

Conclusion

Metals which cause cancer are mostly elements and human beings get exposed to these elements through different means including (but not limited to) air, contaminated drinking water, occupational settings and the consumer products. Studies on how different types of cancer are caused have established the fact that there is a relationship between cancer and heavy metal like nickel, cadmium and arsenic. Toxic heavy metals cause different diseases in human beings and animals. These heavy metals produce ROS and damage DNA of the cell. Different heavy metals have different tendency in human beings and animals. High exposure of arsenic (As) cause skin disorder, cancer, brain disorder, cardiovascular disorder and diabetes, chronic effect cause by lead, mercury damage our brain, kidney. Cadmium inhibits the repairing of DNA, high level of aluminium loss the memory, over intake of iron causes DNA damage. Biomedical studies have established the fact that on the repair pathways of DNA. At very low quantity arsenic, nickel and cadmium may have an important role in metal-associated cancer and stop the formation of individual DNA repair protein. It means human health is affected even at low doses of nickel and cadmium. DNA repair proteins. Multiple mechanisms are followed by metal-induced carcinogenesis are induced. Metal-induced carcinogenesis is followed by various mechanisms. Alu/Alu recombination is also a factor which contributes significantly to this process.

References

1. Bennett LE, Burkhead JL, Hale KL, Tery N, Pilon M, et al. (2003) Analysis of transgenic Indian mustard plants for phytoremediation of metal contaminated mine tailings. J Environ Qual 32: 432-440.
2. Morales E, Cathrine MA, Jonathan CO, Jereny S, Prescott LD, et al. (2016) Heavy metals exposure influences double strand break DNA repair outcomes. Plos One, pp: 1-21.
3. Tasleem JA, Mudsser A, Kehkasha S, Arif A, Inho C, et al. (2015) Heavy metals and human health, mechanistic insight into toxicity and counter defence system of antioxidant. Int J Mol Sci 16: 29592-29630.
4. Ikhuoria EU, Okieimen FE (2000) Scavenging cadmium, copper, lead, nickel and zinc ions from aqueous solution by modified cellulosic sorbent. Int J Environ Stud 57: 401-409.
5. Sahu RK, Arora NK (2008) Bioassay as a tool for assessing susceptibility and resistant plant species for field contaminated with industrial effluents. World J Microbiol Biotechnol 24: 143-148.
6. Jaishankar M, Mathew BB, Shah MS, Murthy KTP, Gowda SKR (2014) Biosorption of few heavy metal ions using agricultural wastes. J Environ Pollut Hum Health 2: 1-6.
7. Meharg AA (2004) Arsenic in rice-understanding a new disaster for south-east Asia. Trends Plant Sci 9: 415-417.
8. Cheng SP (2003) Heavy metal pollution in China: Origion, pattern and control Environ. Sci Pollut Res Int 10: 192-198.
9. D'Souza C, Peretiatko R (2002) The nexus between industrialization and environment: A case study of Indian enterprises. Environ Manag Health 13: 80-97.
10. Flora SJS, Mittal M, Mehta A (2008) Heavy metal induced oxidative stress and its reversal by chelation therapy. Ind J Med Res 128: 501-523.
11. Jan AT, Ali A, Haq QMR (2011) Glutathione as an antioxidant in inorganic mercury induced nephrotoxicity. J Postgrad Med 57: 72-77.
12. Chen CW, Chen CF, Dong CD (2012) Distribution and accumulation of mercury in sediments of Kaohsiung River Mouth. Taiwan APCBEE Procedia, pp: 153-158.
13. Jan AT, Murtaza I, Ali A, Haq QMR (2009) Mercury pollution: An emerging problem and potential bacterial remediation strategies. World J Microbiol Biotechnol 25: 1529-1537.
14. Chang LW (1977) Neurotoxic effects of mercury: A review. Environ Res 14: 329-373.
15. Asano S, Eto K, Kurisaki E, Gunji H, Hiraiwa K, et al. (2000) Acute inorganic mercury vapour inhalation poisoning. Pathol Int 50: 169-174.
16. Bates N (2003) Metallic and inorganic mercury poisoning. Emerg Nurse 11: 25-31.
17. Clarkson TW (1993) Mercury: Major issues in environmental health. Environ Health Perspect. 100: 31-38.
18. Farina M, Aschner M, Rocha JBT (2011) Oxidative stress in methylmercury induced neurotoxicity. Toxicol Appl Pharm 256: 405-417.
19. Geier DA, King PG, Hooker BS, Dorea JG, Kern JK, et al. (2015) Thimerosal: Clinical, epidemiologic and biochemical studies. Clin Chim Acta 444: 212-220.
20. Hintelmann H (2010) Organomercurials: Their formation and pathways in the environment. Met Ions Life Sci 7: 365-401.
21. Carneiro MFH, Oliveira Souza JM, Grotto D, Batista BL, de Oliveira Souza VC, et al. (2014) A systemic study of the deposition and metabolism of mercury species in mice after exposure to low levels of Thimerosal (ethylmercury). Environ Res 134: 218-227.
22. ASTDR (2015) Toxicological profile for mercury.
23. WHO (2004) Guidelines for drinking-water quality Sixty-first meeting, Rome, 10-19 June 2003 Joint FAO/WHO Expert Committee on Food Additives.
24. Zalups RK, Lash LH (1994) Advances in understanding the renal transport and toxicity of mercury. J Toxicol Environ Health 42: 1-44.
25. EPA (2010) An overview of Airborne Metal Regulations, Exposure Limits, Health Effects and Contemporary Research (Appendix C).
26. ATSDR (2007) Toxicological profile for lead.
27. Langworth S, Elinder CG, Sundquist KG, Vesterberg O (1992), Renal and immunological effects of occupational exposure to inorganic mercury. Br J Ind Med 49: 394-401.
28. Cardenas A, Roels H, Bernard AM, Barbon R, Lauwerys RR, et al. (1993) Markers of early renal changes induced by industrial pollutants I Application to workers exposed to mercury vapor. Br J Ind Med 50: 17-27.
29. Franko A, Budihna MV, Dodic-Fikfak M (2005) Long-term effects of elemental mercury on renal function in miners of the Idrija Mercury mine. Ann Occup Hyg 49: 521-527.
30. Al-Saleh I, Al-Sedairi A, Elkhatib R (2012) Effect of mercury (Hg) dental amalgam fillings on renal and oxidative stress biomarkers in children. Sci Total Environ 431: 188-196.
31. Li Y, Zhang B, Yang L, Li H (2013) Blood mercury concentration among residents of a historic mercury mine and possible effects on renal function: A cross sectional study in south western China. Environ Monit Assess 185: 3049-3055.
32. Zalups RK (2000) Molecular interactions with mercury in the kidney. Pharmacol Rev 52: 113-143.
33. Zalups RK, Barfuss DW (1990) Accumulation of inorganic mercury along the renal proximal tubule of the rabbit. Toxicol Appl Pharmacol 106: 245-253.
34. Zalups RK (1991) Method for studying the *in vivo* accumulation of inorganic mercury in segments of the nephron in the kidneys of rats treated with mercuric chloride. J Pharmacol Methods 26: 89-104.

35. Tanaka-Kagawa T, Naganuma A, Imura N (1993) Tubular secretion and reabsorption of mercury compounds in mouse kidney. J Pharmacol Exp Ther 264: 776-782.

36. DeCeaurriz J, Payan JP, Morel G, Brondeau MT (1994) Role of extracellular glutathione and γ-glutamyltranspeptidase in the disposition and kidney toxicity of inorganic mercury in rats. J Appl Toxicol 14: 201-206.

37. Zalups RK (1995) Organic anion transport and action of g-glutamyltranspeptidase in kidney linked mechanistically to renal tubular uptake of inorganic mercury. Toxicol Appl Pharmacol 132: 289-298.

38. Zalups RK, Barfuss DW (1998) Participation of mercuric conjugates of cysteine, homocysteine and N-acetylcysteine in mechanisms involved in the renal tubular uptake of inorganic mercury. J Am Soc Nephrol 9: 551-561.

39. Cannon VT, Zalups RK, Barfuss DW (2000) Molecular homology and the luminal transport of Hg^{2+} in the renal proximal tubule. J Am Soc Nephrol 11: 394-402.

40. Zalups RK (1998) Basolateral uptake of inorganic mercury in the kidney. Toxicol Appl Pharmacol 150: 1-8.

41. Bridges CC, Zalups RK (2005) Molecular and ionic mimicry and the transport of toxic metals. Toxicol Appl Pharmacol 204: 274-308.

42. Torres AM, Dnyanmote AV, Bush KT, Wu W, Nigam SK (2011) Deletion of multispecific organic anion transporter (Oat1/Slc22a6) protects from mercury-induced kidney injury. J Biol Chem 286: 26391-26395.

43. Bridges CC, Zalups RK (2010) Transport of inorganic mercury and methylmercury in target tissues and organs. J Toxicol Environ Health Crit Rev 13: 385-410.

44. Bridges CC, Joshee L, Zalups RK (2008) Multidrug resistance proteins and the renal elimination of inorganic mercury mediated by 2, 3-dimercaptopropane-1-sulfonic acid and meso-2, 3-dimercaptosuccinic acid. J Pharmacol Exp Ther 324: 383-390.

45. Compeau GC, Bartha R (1985) Sulfate-reducing bacteria: Principal methylators of mercury in anoxic estuarine sediment. Appl Environ Microbiol 50: 498-502.