Metabolic Toxicity and Alteration of Cellular Bioenergetics by Hexavalent Chromium

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Abstract

Extensive industrialization, exhaustive mining, and whirlwind urbanization disseminate deep impact upon the world's living being since dawn of the modern civilization. The consequences of all these environmental and anthropogenic

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attributions in the atmosphere lead toward non-returnable noxious situation. Both intentional and accidental activities of human accelerate environmental degradation via release of pollutants and give a momentum in gradual bioaccumulation of toxicants in the food chain resulting in deleterious feedback to its creator in terms of hazardous and toxic health manifestations. Cr(VI) is an industrial, anthropogenic, and airborne environmental toxicant that acquires to have carcinogenic, genotoxic, and organ-specific irreversible complications. Due to its high diffusional proficiency, Cr(VI) penetrates into the cellular compartments through phosphate and sulfate anion exchange carriers. Cr(VI), being a potential oxidizing agent for organic compounds and strong free radical generator in the biological system, gets oxidized by ascorbic acid and glutathione and liberates different reduced forms of chromium. These in turn stimulate ample amount of free radical formation through Fenton reaction. Cellular macro- and micromolecules are very much delicate and sensitive to these free radicals like ROS, RNS, and singlet oxygen species which interrupt their normo-physiological purpose. Being a potent neurotoxic and antioxidant suppressive agent, Cr(VI) enhances lipid peroxidation and other neurological complications among the exposed organisms. Recently it has been also enlisted in the endocrine disruptor chemicals thus executing its hormonal and developmental toxicities. Through reduction of antioxidant level and flavoenzyme activity, Cr(VI) expresses sensitive mutational, structural, and regulatory intervention inside the cells. Cr(VI) promotes posttranslational modification principally by abnormal glycosylation which conveys conformational changes in active biomolecules and biological catalysts. Metabolism is an organized series of life-sustaining biochemical transformation of crucial biomolecules within the cells. Cr(VI) insensitively acts on metabolic pathways by altering the enzymological parameters, shifting the conformational architecture of enzymes as well as by exhaustion of substrate level in the cytoplasm. Cr(VI) toxicity compels significant depletion of glycolytic substrate and end products inducing hypoglycemic situation in the organism. Additionally, it also affects the glycogenolytic activity in the muscle and liver. The principal mitochondrial energy-generating pathways, viz., TCA cycle and oxidative phosphorylation, are found to be suppressed due to Cr(VI) toxicity in hepatic, muscular, renal, and cerebral tissue. The linking enzymes of cytoplasmic and mitochondrial metabolic pathways such as lactate dehydrogenase and pyruvate dehydrogenase are adversely affected by Cr (VI) toxicity. Different proteolytic enzymes and their activities as well as substrates of protein metabolism along with transaminase enzyme activity are notably altered in the organism owing to exposure of this heavy metal. Thus Cr(VI) toxicity prominently disturbs metabolic integration and subsequently alters cellular bioenergetics in the mammalian system.

Keywords
Hexavalent chromium · Cellular bioenergetics · Carbohydrate metabolism · Protein content · Protease activity · Serum lipid profile · Fatty acid synthase

Introduction

Metal toxicity, a global concern, comes into picture from the very commencement of the so-called civilization which the human bore for their benefit and exposed for different purposes. From the dawn of industrialization in the eighteenth century to the present times, anthropogenic activities have triggered accumulation of huge amount of pollutants and industrial effluents to the environment (Steffen et al. 2015). The long-run effect of the atmospheric pollutants and toxicants leads to ecosystem imbalance, increases earth temperature, enhances evolutionary mutations in microorganisms, induces irreversible health complications, deteriorates atmospheric air particulate nature, and, last but not the least, causes severe and concerning global impact (Gunther and Hellmann 2017). Concomitant with development of science and technology, the use of metals has increased vigorously and simultaneously offers a dangerous and never-ending consequence of environmental plunders to the biosphere. Metal pollution has been amplified globally in a significant manner as an effect of industrialization since the late nineteenth and early twentieth century. The widespread application of the metallic ores and metalloids produces an alarming environmental situation with its efflux and effluents exposed to the organism through occupational, accidental, inhalational, and contact absorption (Yadav et al. 2017). Metals in their transitional form act as trace element in the animals' and plants' nutrition but in the valence state become toxic at a critical amount. Some heavy metals such as chromium, cobalt, mercury, cadmium, lead, etc. are important to note as these cause severe toxicity to the exposed organisms (Wang et al. 2012; Das and Pal 2017).

Chromium (Cr) is a naturally occurring transition metal usually found in rocks, volcanic eruption, soil, as well as plant and animals. Chromium acquiring a molecular weight of 59.54 with 44 electrons in the electron shell can exist in several valence states. It can appear in the environment in organic and also as inorganic form; the organic form acts as trace element for the benefit of organisms, but the inorganic salt form is much toxic due to its powerful redox potential. Chromium exists in various oxidation states from divalent to hexavalent state (Doisy et al. 2013). Potassium dichromate ($K_2Cr_2O_7$) and sodium chromate (Na_2CrO_4),two important inorganic salts of hexavalent chromium [Cr(VI)], have been widely used in numerous industrial processes such as metallurgy, chrome plating, chemical industry, textile manufacture, wood preservation, photography and photoengraving, refractory and stainless steel industries, and cooling systems (Park et al. 2004).

The inappropriate use, disposal, and management of these products lead to heavy metal pollution that is a serious concern worldwide. Seven countries – South Africa, India, Kazakhstan, Zimbabwe, Finland, Brazil, and Turkey – which are leaders in terms of chromium pollution, produce large amount of industrial effluents containing Cr(VI) (Mishra and Malik 2012). India is the third and most important exporter of the chromium ore in the global scenario. It contributes 19% of world production, of which 99% is mined from Odisha where a huge number of opencast chromium mines meet the export demand throughout the year (Soudani et al. 2012; Mishra et al. 2016). Chromium compounds have various industrial applications including

tanning, corrosion inhibition, plating, glassware cleaning, safety match manufacturing, metal finishing, and pigments where high concentration of chromium (40–50,000 ppm) has been reported in the effluents of these industries (Park et al. 2004). The most important feature of chromium's toxicity is its persistence in the environment and its existence in several form and valence states. The hexavalent form, Cr(VI), leaches to the water bodies and penetrates to the groundwater level causing acute toxicity via contact, use, and consumption of natural water.

Cr(VI) can penetrate through the cell membrane more easily than the other chromium compounds thus executing its potential toxic manifestation; the severity of chromium toxicity depends on its valence state. Chromate and dichromate are highly soluble in water and thus readily absorbed by the gastrointestinal tract due to its high diffusional capacity through all types of cell membrane (Clarkson 1993). Once inside the cell, Cr(VI) is metabolized to trivalent chromium, either enzymatically (via microsomal enzymes) or nonenzymatically (via ascorbate and GSH). The liver is the main organ responsible for the metabolism, detoxification, and secretory function of the organism; it regulates plenty of metabolic pathways of mammalian systems including metabolic interconversion of Cr(VI) to Cr(III). The primary transmit of this toxicant is inhalation (Bagchi et al. 2002); other probable forms include oral ingestion of contaminated water or direct dermal contact with products manufactured using chromium such as pressure-treated wood, paint, welding materials etc. (Ahmed et al. 2014). Of the several valence forms, Cr(0), Cr(III), and Cr(VI) predominate, yet only Cr(VI) is found to be carcinogenic as well as mutagenic and also abundant in natural water (Bagchi et al. 1997, 2000). The diffusible form of chromium as Cr(VI) accumulates in various tissues of the exposed organism and executes patterns of cellular toxicity, disrupts normal morphophysiological prototype of cellular integrity, and seriously disturbs biochemical as well as enzymological functions related to the metabolic process (Arslan et al. 1987). Cr(VI) causes several health complications ranging from chronic skin to malignant cancer (Naz et al. 2016). Cr(VI), being a potent oxidative stress modulator and apoptotic signal enhancer in the renal tissue, significantly executes acute renal damage and advanced tubular necrosis in mammalian systems of the experimental animal (Hegazy et al. 2016). Genotoxicity of Cr(VI) is well evident by formation of excessive free radicals and by producing DNA cross-linking, DNA protein cross-binding, chromosomal aberration, and genomic instability in the nuclear environment of the specific cells (Velma and Tchounwou 2013).

Basics of Cellular Bioenergetics

Living organisms are extremely structured and composite creatures. The cell, tissue, and organ systems exhibit unique property to respond to the stimulus from internal and external origin and accordingly alter cellular as well as physiological attribution to cope up with the circumstances and also to maintain equilibrium in cellular context (Alberts 1998). Subsequently organism grows and reproduces, and in the

course of evolution, diversification and speciation occur. All life-sustaining physicochemical responses necessitate sufficient and uninterrupted supply of energy. ATP, the high-energy phosphate molecule, is produced maximally through aerobic oxidation of fuel molecules such as glucose, protein, and fat. Insufficient ATP production due to external or internal factor or genetic shortcoming facilitates alteration in the cellular structure and nature of its functions, i.e., growth, development, repairment, and maintenance of metabolic homeostasis (White 1943). Extraction of energy and transformation into fuel for general functions as a uniform and composite functioning unit are exceptional attributes of all living organisms.

Solar Energy: The Source of Energy for Living Creature

Plants and some photosynthetic bacteria can entrap solar energy and photochemically convert it into food energy for their metabolic purpose as well as to provide energy to the saplings. To accomplish this, carbon assimilation process helps to produce biologically essential macromolecules like glucose, amino acids, etc. in plants. Organisms surviving through holozoic nutrition are incapable to trap solar energy thus dependent on plants and animals to import chemical bond energy to accomplish energy-linked physiological functions (Raubenheimer et al. 2009). Eventually, an organism may get its energy from plant or animal, but the sole source of energy is the solar energy that is circulated from one trophic level to the other through the food chain of ecosystem. Living organisms synthesize energy from organic macromolecules through cellular respiration where oxygen operates a significant role with resultant production of CO_2 and H_2O. Within the cell, mitochondria are considered for the ultimate production house of burning fuel in terms of ATP (Alberts et al. 2013). That ATP is utilized for cellular function to its optimum level by a healthy and energetic tissue. However, unutilized biofuel is preserved in terms of glycogen or lipids for future use in energy-deprived situation (Fig. 1).

Characterization of Energy

Energy can be categorized as the capability to perform work. In biology, work signifies one of the three properties such as chemical work, transport work, and mechanical work. Energy can also be characterized depending on its source, mode of action, and site of action. Different forms of energy are electrical, thermal, and photon energy. All these forms are distinct from each other though share a common characteristic to materialize into two forms, the kinetic energy and potential energy (Barak et al. 1997). Energy of motion is solely related to the kinetic energy, whereas potential energy is depicted as the stored energy. The classical example of kinetic energy in biological context is the transport of molecules across the biological membranes. The important attribution of all types of energy is reversible conversion of potential energy to kinetic energy.

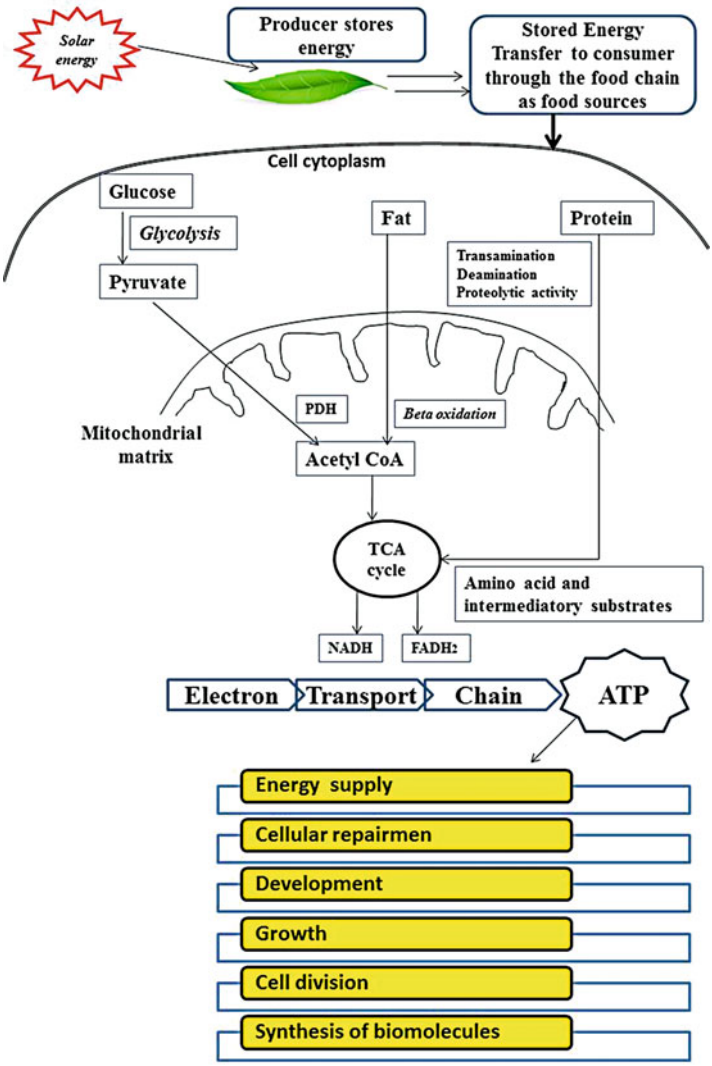

Fig. 1 Major energy source and energy metabolic pathways in organism

Transformation of Cellular Energy: Role of Metabolism

All types of cellular activity require energy through specific metabolic process. Metabolism is a multifaceted network of extremely synchronized biochemical reactions in which the physiological functions proceed inside the cell to make a balance between its demand and supply. Every step of metabolic pathways is a diverse enzymatic reaction considering a specific enzyme, substrate, and definite cofactor. These reactions are of two categories: extraction of energy from calorigenic nutrients

like proteins, carbohydrates, and fats and production of high phosphate molecule and reduced electron acceptor via synthesis or breakdown of the nutrient molecule. Energy from high-energy phosphate bonds of ATP or high-energy electrons of NADPH, $FADH_2$, or NADH is transferred to the covalent bonds of the biomolecules (Alberts et al. 2013). Metabolism has its two wings, the anabolism and catabolism. Anabolic reaction leads to the formation of new molecules partially using the cellular energy with the help of enzymes. On the other hand, catabolism refers to breakdown of one molecule to produce another in response to cellular demand. Catabolic and anabolic reactions happen concurrently in the cells of the organism to maintain homeostasis between breakdown and synthetic phenomena.

Catabolism is processed in two ways using aerobic and anaerobic respiration. Aerobic respiration is economical over the anaerobic reaction for the cells. In aerobic respiration glucose generally pursues two metabolic pathways: glycolysis and citric acid cycle (tricarboxylic acid cycle). The breakdown product of lipid especially glycerol also takes part in glycolytic reactions and finally gives rise to pyruvate. This ensures a metabolic link between carbohydrate and fat metabolism. Pyruvate gets converted into acetyl CoA and afterwards enters into the mitochondrial compartment to participate in TCA cycle. Proteins are dissociated into the amino acids that may act as the intermediates of TCA cycle and provide a metabolic link. On the other hand, fatty acid is also enzymatically catalyzed to acetyl CoA to support TCA cycle. By this way carbon from glycolysis and other metabolic sources enters the TCA cycle thus leading to an interminable cycle of energy production in terms of ATP, NADH, $FADH_2$, and NADPH. The entrapped energy of NADH and $FADH_2$ is transferred through the electron transfer system (ETS) of the inner mitochondria thus producing high-energy phosphate bond of ATP by chemo-osmotic reaction with the help of F_1F_0ATPase enzymatic system (Alberts et al. 2013; Wang and Oster 1998). Any disturbance in energy production imposes imbalance between expenditure and renewal thereby restricting the communication between metabolism and supply of nutrients and essential biomolecules. However, disturbed ETS function within mitochondria may lead to leakage of free electrons that can trigger formation of harmful free radicals especially superoxide anion promoting oxidative stress within the cell.

Chromium: A Transition Metal of Health Concern

Detection

Chromium is the twenty-fourth element in the periodic table in the group of transition metal with molecular weight of 51.99 g/mol and atomic number 24 (Brandes et al. 1956). It is named so due to its multicolored attribute and from Greek word “chroma.” This element generates many beautiful colored compounds naturally assimilating with different types of metals in different ratios. Chromite is a red-colored chromium compound used as the gem stone; moreover the red color of rubies, pink color of sapphire, and green color of emerald are also due to the

presence of certain amount of chromium among their metallic components (Holleman et al. 1985). In early 1761 it was discovered as red-colored crystalline pigment of lead chromate (crocolite). According to archaeologists, in the late third century BC, the Qin Dynasty used terracotta army weapons coated with chromium (Cotterell 2004). Johann Gottlob Lehmann, a German mineralogist and geologist, on July 26, 1761, isolated an orange-red-colored compound from the mine of Beryozovskoye of Ural Mountains which he misidentified as lead-iron-selenium compound, but originally it was lead chromate. Later in 1770, Peter Simon Pallas found a unique compound from the same place Lehman visited and noticed that it contained coloring property that may be used as paints (Guertin et al. 2005). In 1797, Louis Nicolas Vauquelin isolated metallic chromium from Peter's coloring compound with high-temperature oxidation in a charcoal oven, and this finally led to the discovery of chromium metal (Vauquelin 1798). In the eighteenth century, chromium was commonly used in paints and tanning salts, and the production of inorganic compound of chromium salt was initiated (Dennis and Such 1993). Chromium is now commonly used as metal alloys and in industries. Full-fledged uses in stainless steel production and several anticorrosive metals have been practiced now (Nordberg et al. 2014).

The Metal Chromium

Metallic Properties

Chromium is a steel-gray lustrous metal that can be polished to achieve its shiny texture for commercial purpose. It is a very active metal which merely doesn't react with water but reacts with most acids. Oxidation of this element continues in the room temperature and subsequently produces Cr(III) oxide. In a stable environment, the oxidation procedure creates a protective layer that prevents further corrosion of this metal (Brandes et al. 1956).

Magnetic Properties

Elemental chromium contains paramagnetic characteristics. Depending upon the temperature, it shows differing attributes of magnetic properties. Alteration in the temperature affects the electron spinning alignments. Chromium oxide acquires ferromagnetic feature; for this it has the capacity of data tape, a specific way to store information. By differing in the ratio of chromium with other elements, the hybrid compounds can attain magnetic properties. Some stainless steel compounds have magnetic properties that solely correspond to the amount of chromium in them (Ishikawa et al. 1965).

Production, Use, and Human Exposure

Chromium, a mineral of earth crust, is mostly excavated through mining. The total amount of chromium produced is million tons per annum. The principal contributor

of chromium for industrial and other essential purposes is South Africa, India, Kazakhstan, Zimbabwe, Finland, Brazil, and Turkey (Mishra et al. 2016). In India, through opencast mining, maximum amount of chromium is produced in Odisha. Throughout the world, chromium is exported and imported as ferrochrome. Metallic chromium for industrial uses is produced by the reduction of raw chromite ore which is excavated from the mines. Inorganic salts of chromium such as sodium and potassium dichromate are produced by sweltering chromite ore with soda ash, and all these compounds are widely used in leather tanning, wood preserving, photoengraving, and refractory industries. Metallurgical industry mostly uses the metallic chromium for the production of stainless steel, ferrous, and nonferrous alloys (Barnhart 1997) (Fig. 2).

Moreover, chromium introduces itself in the nature from combustion processes mainly as Cr(III) oxide. Cr(VI) has been found in fly ash of power plant systems (Stern 1982). Both of these forms of chromium reach to the water sources leaching from the industrial effluents or from the contaminated soil (Pellerin and Booker 2000). Minor amount of chromium is also contributed through the natural phenomenon such as volcanic eruption and dispersal to soil by wind and rain. By these ways Cr(VI) reaches and accumulates in the groundwater and simultaneously contaminates the drinking water. Several studies confirm that Cr(VI) is found in an extensive amount in the groundwater of the nearby areas of different chromium using industries (Saha and Orvig 2010). The industrial effluents from textile, metallurgy, and leather industries have been illegally dumped into the open environment or in deep burials without proper treatment which ultimately release noxious pollutants including chromium in the environment (Kumar et al. 2008).

The principal way of exposure of Cr(VI) is inhalation followed by ingestion and dermal absorption as well as by the chronic or accidental acute ingestion (ATSDR 2000).

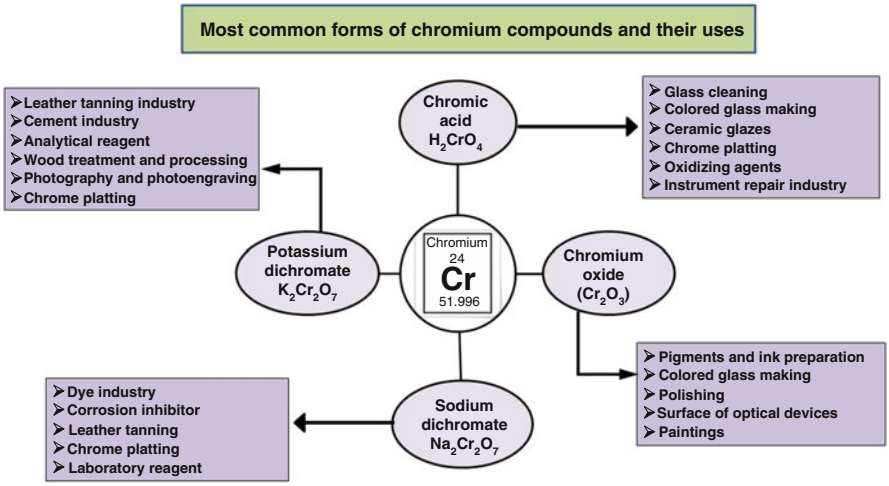

Fig. 2 Different chemical forms of chromium and their sources and uses

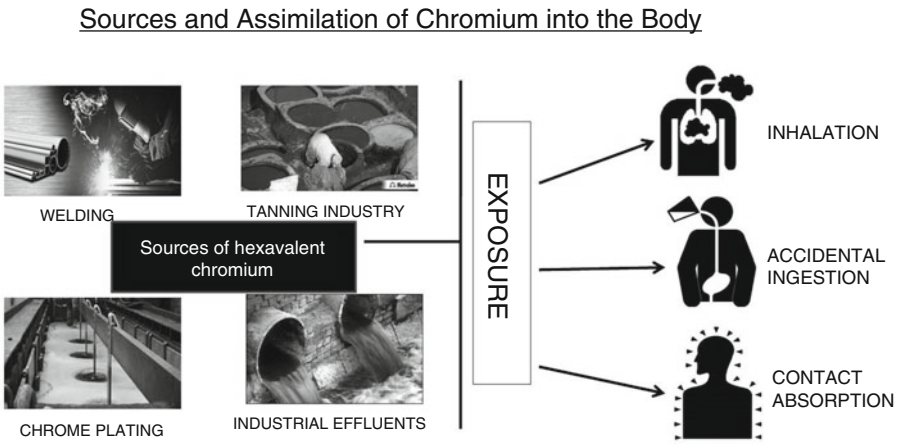

Fig. 3 Exposure of human being to chromium from various environmental sources

Occupational exposure is prominent among the workers of different industries including welders and chrome miners where Cr(VI) is responsible to cause severe health complications to the exposed individuals.

Exposure of this toxic metal to the community takes place through stained foods, contaminated water, and polluted air. The maximum exposure of Cr(VI) becomes apparent to the workers involved in chrome plating and chromate production (ATSDR 2000) (Fig. 3).

Absorption, Distribution, and Metabolism

The absorption of ingested or inhaled Cr(VI) follows certain characters such as oxidation state, solubility, and particle size of the metallic compound (ATSDR 2012). Outsized particles (>10 μm) of Cr(VI) compounds if inhaled are retained mostly in the upper respiratory tract, whereas smaller particles can move toward the lower respiratory tract. A small amount of accumulated Cr(VI) can be reduced to trivalent form (Cr(III)) in the interstitial lining fluids reacting with cellular biomolecules or antioxidant parameters present within the bronchial tree (Petrilli et al. 1986). At physiological pH Cr(VI) attains membrane-penetrable capacity due to its tetrahedral oxy-anions; on the other hand, Cr(III), being of predominantly octahedral configuration, is practically impermeable to the cell membrane. Cr(VI) enters into the cells via nonspecific anion exchangers of sulfur and phosphorus and subsequently is reduced to form chromium derivatives (Arslan et al. 1987) (Fig. 4).

Inhaled Cr(VI) from the lungs reaches to the gastrointestinal tract through mucociliary clearance and gets absorbed there. Within the gastrointestinal tract, the intestinal lining mainly absorbs Cr(VI) compound consumed orally, by dermal contact or by inhalation (Kerger et al. 1997; Kim et al. 2004). According to the recent study, it is found that Cr(VI) is easily absorbed through the oral administration

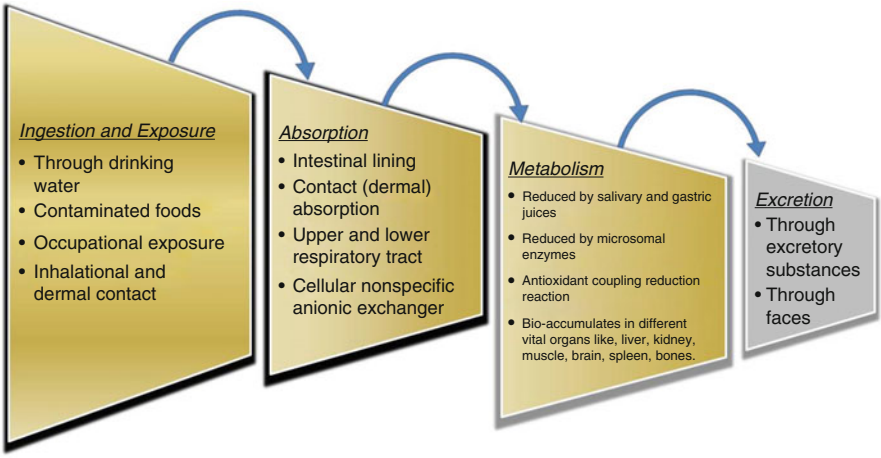

Fig. 4 Pharmacokinetics of hexavalent chromium compounds

to the experimental animal (ATSDR 2000). After entering into the cellular atmosphere, Cr(VI) is sequentially reduced to Cr(V), Cr(III), and Cr(IV) reacting with cellular antioxidants and ascorbic acid (Sehlmeyer et al. 1990). Among these Cr(VI) is more efficiently absorbed than any other form of chromium due to its high diffusional capacity and enters into the cell via nonspecific anion channels; on the other hand, Cr(III) is taken up by the cells through phagocytosis or by passive diffusion thus penetrating in negligible amount inside the cells (ATSDR 2000). Additionally, little amount of Cr(VI) is reduced by salivary and gastric juices by the reductive elements present in their specific compositions and ultimately excreted through the feces. The absorbed amount of Cr(VI) comes to the blood stream and gets distributed throughout the body, deposited among the tissues, and the rest is excreted through urine (Costa 2003). Bioaccumulation of Cr(VI) occurs irrespective to the organs and organisms exposed to this toxic heavy metal though larger amount of Cr(VI) is found to be deposited in the liver, kidney, spleen, and osseous tissue (Kargacin et al. 1993; Mancuso 1997) (Fig. 5).

General Health Effects of Chromium

Organic form of chromium comprises of Cr(III) present in dietary vegetables, fruits, and animal sources (Smart and Sherlock 1985). Cr(III) is very much essential for the carbohydrate and fat metabolism and regarded as the trace element of the tissue (Anderson 1998). Oral administration of Cr(III) in trace amount doesn't show any toxicity, but prolonged medication of it may have some adverse health effect to the individuals (Elbetieha and Al-Hamood 1997). By contrast exposure of Cr(VI) produces severe organ toxicity, carcinogenicity, and toxic exaggeration of metabolic parameters and enzymatic profiles (Abreu et al. 2014).

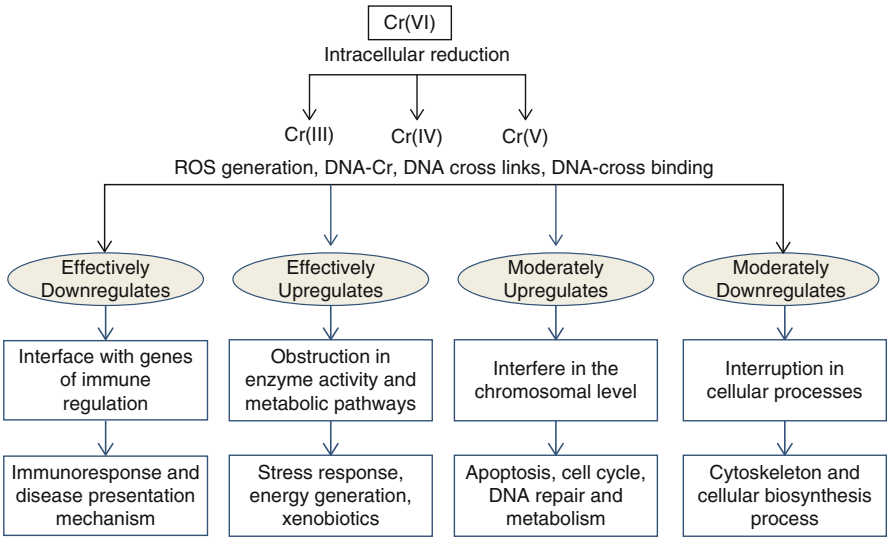

Fig. 5 Some adverse effects of chromium compounds at a glance

Long-term exposure of hexavalent chromium may result in dermatitis, skin rash, and ulceration of nasal mucous membrane of the exposed individuals (Saha et al. 2011). Chromium-handling workers of different factories may have common complaints of allergic sensitization (Shelnutt et al. 2007). Additionally, Cr(VI) causes organ toxicity depending on its duration of exposure and degree of deposition within organs. In hepatocytes it causes cytoplasmic vacuolization, hepatocellular inflammation, and steatohepatitis of the exposed organism and is also responsible for systemic organ dysfunction (Costa 2003). Nephrotoxic effect of Cr(VI) is observed among occupationally exposed individual in terms of excessive fat deposition in different regions of the kidney with severe deregulation of metabolic pathways (Kumar and Rana 1984). Proteinuria and oliguria associated with nephrocellular abnormality are the distinctive features of Cr(VI)-assisted kidney toxicity (Diaz-Mayans et al. 1986). Hematological parameters, including respiratory pigment and soluble antibodies of body fluid, drastically changed due to the Cr(VI) intoxication (Costa 2003). Intracellular reduction product of Cr(VI) has greater affinity to react with cellular macromolecules causing several biochemical obstructions inside the cells including carcinogenicity, mutagenicity, and chromosomal aberrations (Zhitkovich 2011). Moreover, Cr(VI) seems to bioaccumulate in a great extent in different segments of nervous system and creates irreversible toxic manifestations in a proportion to the percent of Cr(VI) accumulation (Nudler et al. 2009).

The hexavalent chromium enters into the cellular structure and produces irreversible toxic derangement to the cellular conformity resulting in the devastating ending of the target tissue (Kirman et al. 2017). Recent studies show that Cr(VI) exerts neurotoxic effect on mature neuronal cell and brain tissue and subsequently fluctuates physiochemical function of the nervous system and brain (Dashti et al. 2014;

Singh and Chowdhuri 2016). Moreover, Cr(VI) hoarding in rat hypothalamus, anterior pituitary, and hepatic as well as muscular tissue implements toxic infestations among these tissues (Quinteros et al. 2007).

Heavy metals including chromium directly or indirectly affect immune system and provoke different forms of immune reactions like neoplasia, autoimmune response, allergy, hypersensitivity reaction, and inflammation. Chromium compounds significantly decrease the T and B lymphocyte proliferation in the cellular level during pathogenic or infected condition and produce immune suppression. Lower doses of Cr(VI) through inhalation elevate phagocytic activity of alveolar macrophages, whereas higher dose of this metal trims down macrophage's functionality. Therefore, Cr(VI) is responsible for dwindling of humoral immunity among the exposed organism. Antigenic substances or pathogen entry into the cell activates macrophages which result in the formation of nitric oxide and function as cytotoxic, antimicrobial, and antihelminthic agents (Mac-Micking et al. 1997). Study reports exhibit that Cr (VI) deliberately interferes with nitric oxide formation by macrophage cells of the exposed tissue (Srivastava et al. 2014). Moreover, chrome-cobalt alloy proliferates inflammatory mediators from sensitized macrophages subsequently triggering acute inflammation and necrosis (Cohen et al. 1998). Expression of TNF-α (tumor necrosis factor-alpha), NK cells, lymphocytes, neutrophils, and mast cells that make up acute-phase reactions is found to be suppressed by hexavalent chromium (Jain and Kannan 2001). Toxic exposure of Cr(VI) produces retardation in the quantity of splenocytes and spleen weights and resultant decline in the blood lymphocytes thus interfering with the blastogenesis and immunoglobulin formation (Borella et al. 1995). Thus Cr (VI) affects different forms of immunogenic molecules and vital immune pathways by suppressing or by reverse modulation of immune response.

Moreover, occupational, environmental, or accidental exposure of endocrine disruptor chemicals (EDCs) has been associated with numerous reproductive and physiological abnormalities. Cr(VI) has been recognized as a endocrine disruptor used by several industrial processes which contribute to chemical abundance in the atmosphere. Cr(VI) is evidenced to cause severe reproductive toxicity to the exposed organism irrespective of gender. It produces morphological alteration of the seminiferous tubule with enlarged intracellular spaces, prominent decline in sperm count and motility, and toxic changes in epididymal spermatozoa and Leydig cells' architecture (Marouani et al. 2017). Reproductive hormones are very much sensitive to EDCs and supposed to act randomly in the presence of these chemicals. In connection with this, it is found that gestational exposure of Cr(VI) causes enhancement of germ cell or oocyte apoptosis, deregulates the hormonal secretion, disrupts fetal development, and produces fetal organ malformation (Gale 1978). Additionally, Cr(VI) can cross the blood-brain barrier and is also able to pass from mother to offspring through breastfeeding (Samuel et al. 2014). Cr(VI) significantly accumulates in the testis, ovary, and fetus if exposure occurs during gestational periods (Trivedi et al. 1989). It is also responsible for the alteration of steroid and peptide hormones and depletion of antioxidant and enzymatic entity of testicular and ovarian tissues (Banu et al. 2011). Alteration in histoarchitecture and extension of the estrous cycles in the organism are also noted in hexavalent chromium intoxication (Murthy et al. 1996).

However, metabolic alterations are the important phenomena by which most of the metals or metalloids including chromium exert their toxic manifestations. Few reports are available supporting the metabolic perturbation in chromium intoxication (Tajima et al. 2010; Pan et al. 2012; Xiao et al. 2012). Cr(VI) exerts its harmful effects by altering the metabolic parameters in the organism exposed to this noxious element. It alters enzyme expression by inhibiting enzyme's activity or by diminishing functional attribution of crucial enzymes. It mimics property of some anions that may influence specific binding capacity of certain enzymes resulting in disturbance of the enzymes' general biochemical activity. Additionally, Cr(VI) significantly depletes sulfur ions from the cellular compartments and prominently deregulates different metabolic enzymes that are selectively dependent upon the sulfur ions for their active participation in the metabolic reactions (Holland and Avery 2011). It was also responsible for the toxic alteration of enzyme expression at mRNA level in different tissues (Abreu et al. 2014) and actively deteriorates the metabolic functionality of different enzymes.

Chromium as an Oxidative Stress-Producing Molecule

Cr(VI) is a potent oxidative stress modulator. Intracellular reduction of the Cr(VI) liberates huge amount of free radicals, reactive oxygen species, reactive nitrogen species, and superoxide anion molecules. All these harmful radicals attack macro- and micromolecules of body fluid as well as cellular compartments (Soudani et al. 2012). Surge of free radicals and stress molecules in response to chromium toxicity is responsible for the increased lipid peroxidation in the exposed tissue. Nervous system, being delicate in structure, is very sensitive to the oxidative stress molecules like ROS and RNS and eventually amplified lipid peroxidation and biochemical alteration of nervous tissue (Quinteros et al. 2008). In this connection, an earlier study stated that the treatment with Cr(VI) could lead to lipid peroxidation in mammalian cerebral tissue (Bagchi et al. 2002). Sub-chronic exposure of Cr(VI) shows significant decline in the level of antioxidant parameters of the liver and parallel increase in the lipid peroxidation indicative of oxidative damage in tissue (Bagchi et al. 2001). These findings thus strongly recommend that Cr(VI) somehow disturbs the mitochondrial electron transport chain to leak out free electrons that initiate excess free radical formation.

Chromium: A Potential Metabolic Disruptor

Environmental toxicants are well-defined oxidative stress generator, mutagenic, and extremely accountable for the alteration of physiochemical and primary metabolic parameters. Non-biodegradable toxicants including heavy metals such as Cr(VI), arsenic, lead, etc. enter easily into the organisms through inhalation, drinking water,

or incidental chronic ingestion which ultimately accumulate inside the organisms affecting crucial biomolecules and enzymatic functions (Soudani et al. 2013). Alteration in metabolic integrity among liver and kidney tissue is reported after hexavalent Cr(VI) treatment for 30 days (Shil and Pal 2017a, b). Subacute Cr(VI) exposure does not exhibit significant effect on gain in body weight, whereas mild increase in liver somatic index (LSI) and kidney somatic index (KSI) is reported in Cr(VI)-exposed mice (Shil and Pal 2017a, b). Increase in LSI after Cr(VI) exposure may result from fatty inflammation in hepatic tissue as a result of toxic injury imposed by Cr(VI) (Pedraza-Chaverri et al. 2008). Overaccumulation of Cr(VI), hyalinization of the glomerulus, and nephrocellular hypertrophy may be the possible reasons for increasing the KSI of chromium-exposed animals (Li et al. 2016). Cr(VI) is associated with overproduction of free radicals and other stress molecule lineages, consequently responsible for cellular hypertrophy (Ben-Hamida et al. 2016) that may be one of the important causes of increased LSI and KSI. The liver and kidney being chief detoxifying organs of the body generally take the overload of many environmental toxicants and thus become more vulnerable when there is deficit in cellular defense system. In a previous study, significant bioaccumulation of Cr(VI) had been noted in the renal tissue after subacute chromium toxicity that had been correlated with the metabolic and functional abnormalities of the kidney (Shil and Pal 2017b). It is well reported that biomagnification of Cr(VI) occurs in the organism exposed to this toxic metal either occupational, environmental, or accidental (Batvari et al. 2016). This accounts the viable toxic effects to the respective tissues in the Cr(VI)-treated animal.

Role of Hexavalent Chromium in Carbohydrate Metabolism

Carbohydrate depletion is an important toxic manifestation of short-term exposure of hexavalent chromium supported by marked decrease in liver glycogen and pyruvic acid contents in mice model (Shil and Pal 2017a; Vutukuru 2005). Additionally, Cr(VI)-induced hypoglycemia in mice is evident from a dose-dependent study (Shil and Pal 2017a) which may result from renal glycosuria caused by impairment of renal reabsorption of glucose. In this connection, nephrotoxic manifestation of chromium cannot be ignored (Hegazy et al. 2016). It is reported that the kidney is one of the major target organs for many toxic substances, and within it the proximal tubule epithelium is the most important target site of toxicant-induced cell damage (Bashandy et al. 2016). The depressing effect of Cr(VI) on liver and muscle pyruvic acid content may be explained by the fact that glucose that was produced by increased glycogenolytic activity of liver was released immediately to the blood, and this in turn may reduce the accumulation of pyruvic acid in the hepatic tissue by lowering the glycolytic activity (Shil and Pal 2017a). Retardation of glycolytic activity by Cr(VI) may also result from reductive conversion of hexavalent Cr (VI) to trivalent Cr-ATP complex formation that behaves as competitive inhibitor for various ATP-dependent enzymes and several kinases involved in glycolysis as well as TCA cycle (Lippard and Berg 1997; Myers et al. 2011; Ahmad et al. 2011).

Additionally, this decrease in glycolytic activity in observed tissues may be an effect of hypoglycemia induced by Cr(VI). This is evident from the fact that glucagon, a hormone secreted during hypoglycemia, activates a protein kinase that phosphorylates hepatic L-isozyme of pyruvate kinase to inhibit it and thereby retarding glycolysis (Myers et al. 2011). On the other hand, accumulation of lactic acid in the renal tissue that is associated with enhanced LDH activity following chromium intoxication suggests that utilization of pyruvate as the substrate for LDH is triggered to switch over aerobic to anaerobic pathway (Shil and Pal 2017b).

Hexavalent Chromium as Modulator of Glycolytic, Gluconeogenic, and TCA Cycle Enzymes

Alteration in the bioenergetics in the various tissues may be due to abnormal activities of proteins which are directly involved in the metabolic pathways or due to altered substrate availability in the tissue for specific enzyme action (Pauls et al. 1986; Lippard and Berg 1997). Hexavalent chromium is reported to reduce hepatic lactate dehydrogenase (LDH) activity (Shil and Pal 2017a). LDH, being a key enzyme of metabolic link between glycolysis and TCA cycle, is involved in conversion of pyruvate to lactate and thus acts as a good indicator of cellular damage. Suppressed LDH activity by Cr(VI) may result from decreased availability of pyruvic acid as substrate in the hepatic tissue. Another suggestive mechanism of reduced LDH activity may be the leakage of this enzyme from the hepatic tissue as a result of toxic injury imposed by Cr(VI). Toxic damage of the hepatic tissue was indicated by defaming of its actual cellular structure by Cr(VI). Inhibited LDH activity by Cr(VI) was also observed in teleost fish hepatocytes and in renal tissue at sub-chronic exposure (Venugopal and Reddy 1993) and also in hepatocytes of the African catfish at subacute exposure (Kori-Siakpere et al. 2006).On the other hand, elevated LDH activity in the kidney following subacute chromium exposure may result from metabolic shift from aerobic to anaerobic pathway due to less supply of oxygen to the energetically exhausted renal tissue (Shil and Pal 2017b). Additionally, pyruvate dehydrogenase (PDH) activity was found to be decreased in renal tissue of mice exposed to 10 mg per kg body weight of Cr(VI) per day for a period of 30 days. This may in turn perturb the metabolic link between glycolysis and TCA cycle. On the other hand, certain gluconeogenic enzyme activities are also disturbed by short-term chromium exposure in animal model. Glucose 6-phosphatase (G 6-pase) and glucose 6-phosphate dehydrogenase (G 6-PD) activities were downregulated by Cr(VI) in mice kidney (Shil and Pal 2017b). This indicates less supply of calorigenic substrates from noncarbohydrate source in the renal tissue thus making the tissue energy deficient.

Effect of Cr(VI) on certain enzymes of TCA cycle has been documented in animal model. Succinate dehydrogenase (SDH), isocitrate dehydrogenase (IDH), and malate dehydrogenase (MDH) are the important enzymes of the TCA cycle that play a crucial role in ATP or energy generation in all vital organs of the individuals. Hexavalent Cr(VI) exposure at subacute dose and duration exerts negative impact on succinate dehydrogenase enzyme activity in the hepatic and renal tissue thus hampering the ATP production because this enzyme not only plays important role in

TCA cycle but also acts as a potential component of the mitochondrial electron transport chain (Shil and Pal 2017a, b). Suppressed energy production may trigger anaerobic metabolism in the affected tissue following Cr(VI) treatment. That TCA cycle is impaired by Cr(VI) treatment was also evident from the earlier observation (Molina-Jijon et al. 2011). Insufficient compensation by fermentation and inhibition of cellular respiration by hexavalent Cr(VI) cause imbalance in the nucleotide pool and ultimately obliterate the homeostasis of the energy status in Cr(VI)-intoxicated organs of the Cr(VI)-treated animals (Abreu et al. 2014).

Moreover, Cr(VI) exerts powerful inhibition on mitochondrial dehydrogenases such as NADH dehydrogenase (mitochondrial complex I) and succinate dehydrogenase (mitochondrial complex II) which in turn causes depletion of NADH pool from the tissue (Ryberg and Alexander 1990; Bianchi et al. 1982; Shil and Pal 2017a, b). Significant decrease of mitochondrial enzymes in all of these target organs due to Cr(VI) toxicity indicates significant deterioration of the intracellular NADH pool and ATP production in that specific tissue. Less availability of NADH may also contribute to retardation of anaerobic conversion of pyruvate to lactate via suppressed activity of LDH (Table 1).

Recent studies from our laboratory reveal that the activity of malate dehydrogenase (MDH) in mitochondrial isolate was increased in the liver, whereas it was decreased in the kidney (Shil and Pal 2017a). MDH, being a TCA cycle enzyme, also helps in gluconeogenesis to produce glucose from noncarbohydrate source (Bianchi et al. 1982). In this regard, oxaloacetate, the TCA cycle intermediate which is produced from pyruvate in the mitochondria by pyruvate carboxylase, is reduced to malate before leaving the inner mitochondrial membrane, and mitochondrial MDH helps in this reduction process. As Cr(VI) exposure causes hypoglycemia, the gluconeogenic activity of the liver may be stimulated to replenish the loss of blood glucose level. On the other hand, decreased mitochondrial MDH activity in renal tissue by Cr(VI) exposure indicates suppressed metabolic conversion of malate to oxaloacetate in TCA cycle, which may contribute to low energy supply to that specific tissue as a result of toxic insult (Abreu et al. 2014).

Effect of Hexavalent Chromium on Protein Metabolism

Effect of Cr(VI) on Tissue and Serum Protein Content and Free Amino Acid Nitrogen Level

Protein depletion is a serious metabolic imbalance in the hepatic and renal tissue due to Cr(VI) toxicity. Protein depletion in the affected tissue indicates the physiological approach to compensate energy demand or get adapted to the changed metabolic system which may lead to the stimulation of degradation processes such as proteolysis and utilization of degraded products for increased energy metabolism (Begam and Vijayaraghavan 1996; Palanisamy et al. 2011). The reduction of total protein content may be due to the breakdown of tissue proteins under the effect of heavy metal which in turn increased the free amino acid nitrogen concentration in various tissues (Shakoori et al. 1994). Earlier observation of Chandravarthy and Reddy

Table 1 Cr(VI)-induced alteration of carbohydrate metabolism

Carbohydrate metabolism	
Hexavalent chromium intoxication	Blood glucose level decreased (hypoglycemia) (Sastry and Sunita 1983)
	Pyruvate content decreased in liver and kidney tissue (Shil and Pal 2017a, b)
	Enhanced glycogen breakdown in experimental fish and mouse (Tewari et al. 1987; Shil and Pal 2017b)
	Altered TCA cycle enzymes in liver and kidney tissue (Shil and Pal 2017a, b)
	Decreased NADH dehydrogenase activity or diminished oxidative phosphorylation pathway in the kidney and in cell line (lung cancer cell) (Shil and Pal 2017b; Abreu et al. 2014)
	Lactic acid content increased in kidney tissue (Shil and Pal 2017b)
	Increased glycogenolysis in the renal tissue of mouse and fish muscle (Shil and Pal 2017a; Velma and Tchounwou 2013)
	Decreased glucose 6-phosphatase activity in the kidney tissue (Shil and Pal 2017b)
	Decreased glucose 6-phosphate dehydrogenase activity in the kidney tissue (Shil and Pal 2017b)

(1994) revealed a remarkable decrease in total protein content in fish gill and brain with increased activities of transaminases and proteases on exposure to heavy transitional metal. Enhancement of free amino acid nitrogen level in the hepatic and renal tissues may be ascribed to the enhanced accumulation of protein degradation products after Cr(VI) intoxication or may be due to mobilization of free amino acids from peripheral tissue like skeletal muscle to the liver and kidney for supplying substrates for the synthesis of new proteins (Shil and Pal 2017a, b). Heavy metals are the potential agents for induction of abnormal glycosylation inside the tissue (Ramamurthy et al. 2016). Irregular glycosylated or post-translated protein molecules lose their biochemical capability to perform programmed function of cellular integrity and conjugation with other plasma membrane forming matrix (Brockington et al. 2001; Peharec-Stefanic et al. 2012). It is reported that there is an appreciable decline in different biochemical constituents in various tissues of freshwater fish under Cr(VI) stress (Vutukuru 2005). A group of workers (Kori-Siakpere et al. 2006) observed that the plasma protein was lowered in Cr(VI)-treated animals exposed to subacute dose. Excretion of protein through urine as a consequence of renal tubular damage may be suggested for lowering serum protein concentration following chromium intoxication. This is supported by the fact that subcutaneous Cr(VI) treatment to rat stimulated urinary excretion of protein, creatinine, and urea nitrogen (Kim and Na 1991).

Effect of Cr(VI) on Proteolytic Enzyme Activities

It is established that proteins and proteolytic enzymes are very much sensitive to the heavy metal poisoning (Jacobs et al. 1977), and Cr(VI), being one of them, is widely suspected to impose organ toxicity, genotoxicity, chromosomal aberration, mutational changes, DNA-DNA cross-strand, etc. which may prevent enzyme formation

Table 2 Changes in the protein metabolic parameters due to Cr(VI) intoxication

Protein metabolism	
Hexavalent chromium (Cr(VI)) intoxication	Tissue protein content decreased in the liver and kidney of mice and in fish muscle (Shil and Pal 2017a, b; Vutukuru 2005)
	Pronase and cathepsin activities reduced in the kidney of mice; decreased protease activity in fishes (Shil and Pal 2017b; Tulasi and Rao 2013)
	Trypsin activity increased in the renal tissue of mice (Shil and Pal 2017b)
	Free amino acid nitrogen level increased in the kidney tissue of mice (Shil and Pal 2017b)
	Tissue transaminase activity increased in mice and aquatic animals (Shil and Pal 2017b; Satyaparameshwar et al. 2006)
	Post-translation modification of protein molecules (Bagchi et al. 2001; Abreu et al. 2014)
	Alteration of cellular protein structure (Mishra and Mohanty 2008, 2009)
	Rearrangement of proteomics profile (Guo et al. 2013)

or may enhance depletion of proper metabolic intermediates from the respective tissue (Zhitkovich 2011). In this connection, decreased proteolytic enzyme activities such as trypsin, cathepsin, and pronase have been reported in chromium-stressed mice renal tissue (Shil and Pal 2017b). Heavy metal toxicity can lead to alteration of the structure, permeability, and integrity of cell membranes resulting in diffusion of their enzymes outside the cell (Sternlieb and Goldfischer 1976). Decreased proteolytic enzyme activity in the renal tissue by Cr(VI) may be ascribed to less availability of substrate or defective enzyme synthesis. Alteration in physicochemical properties of proteins may involve excess production of reactive oxygen species, and Cr(VI), being a free radical generator (Quinteros et al. 2007), may contribute to them. These in turn may attribute to reduced level of desired tissue proteins for pronase and cathepsin actions. Over-deposition of Cr(VI) in the target tissue may cause symptomatic damage and negative expression of cellular and biomolecular functions in the specific organ and systems (Table 2).

Effect of Cr(VI) on Transaminase Enzyme Activities

Aminotransferases contribute an important role in amino acid catabolism and play a key role in nitrogen metabolism and energy mobilization (Calabrese et al. 1977). Transaminases such as GPT and GOT activities in the liver and kidney were markedly increased in subacute Cr(VI) toxicity (Shil and Pal 2017a, b). This may be due to increased accumulation of free amino acid nitrogen in those tissues which may contribute more substrates to compensate hypoglycemia as well as for the activity of transaminases. Increased transaminase activity in Cr(VI) toxicity in specific organ is also reported in earlier studies (Soudani et al. 2012; Kim and Kang 2016) reflecting adverse effects of Cr(VI) at tissue level. Earlier report suggested that leakage of tissue transaminase to the serum due to damage of the

affected tissue elevated its level in serum sample of the exposed animals (Kim and Na 1991). Cell membrane damage of the exposed tissue by Cr(VI) involves over-production of lipid peroxides and oxidative stress-mediated degeneration of cellular biomolecules (Bagchi et al. 1995, 1997).

Effect of Cr(VI) on Serum Lipid Profile and Fat Metabolism

Cr(VI) appears to have notable effects on lipid metabolism in exposed animals. It has been already established that heavy metal induces the genes responsible for synthesis of the liver enzymes producing cholesterol (Vinodhini and Narayanan 2009; Harabawy and Mosleh 2014). Cr(VI) exhibits its cytotoxic effect by upregulating cholesterol-synthesizing enzymes resulting in increased cholesterol level in cells (Guo et al. 2013). Accumulation of cholesterol and triglyceride in chromium-exposed tissue is supposed to be involved in fatty infiltration of that tissue. This is supported by the morphological studies of the liver carried out in our laboratory which indicated distinct steatosis characterized by overaccumulation of fat in the liver (Shil and Pal 2017a). In continuation with these studies, very recent observation of ongoing research in our laboratory reveals that the activity of fatty acid synthase is stimulated upon subacute chromium exposure. This may result in synthesis of new fatty acids thus enhancing fat depot within the hepatic cell. Not only these, it may also aid lipid substrates for replenishment of energy deficit caused by depletion of hepatic glycogen and protein following chromium intoxication. Additionally, fat deposition in hepatic tissue may be a compensatory mechanism in response to chromium-induced oxidative stress-mediated degeneration of cellular lipids in the form of lipid peroxides. Heavy metal toxicity increased the level of cholesterol, LDL, VLDL, and triglyceride contents in the treated animals that altered the lipid metabolism associated with declined activity of lipoprotein lipase in the hepatic tissue (Yang et al. 2013). High triglyceride content with associated increased mRNA expression of glycerol-3-phosphate acetyltransferase is also noted in heavy metal intoxication (Larregle et al. 2008). Another suggestive mechanism is that heavy metal like Cr(VI) may induce increased expression of fatty acid synthase and also stimulate isocitrate dehydrogenase activity in the liver tissue to promote lipogenesis as a compensatory mechanism of carbohydrate and protein depletion in Cr(VI) intoxication. Moreover, hypoglycemia generally stimulates the secretion of cortisol that causes breakdown of fat in adipose tissue and mobilizes free fatty acids to the liver, thus promoting the synthesis of triglyceride and cholesterol (Wang et al. 2012); and Cr(VI), being a hypoglycemia-inducible factor, may behave like this (Table 3).

Further investigation recently carried out in our laboratory reveals that serum lipid profile is significantly disturbed by subacute hexavalent chromium exposure in mice model. The findings reveal that total cholesterol, triglyceride, and LDL cholesterol contents of serum are significantly elevated after Cr(VI) intoxication, whereas Cr(VI) causes a decrease in the level of HDL cholesterol in serum of mice. The present study is partially in compliance with earlier

Table 3 Alteration in fat metabolic parameters and Cr(VI) accumulation due to Cr(VI) intoxication

Fat metabolism and bioaccumulation of Cr(VI)	
Hexavalent chromium intoxication	Total cholesterol increased in serum (Kumar and Barthwal 1991; Soudani et al. 2011)
	Serum LDL and triglyceride level increased (Soudani et al. 2011; Yousef et al. 2006)
	Serum HDL level decreased (Soudani et al. 2011)
	Lipid peroxidation increased in the liver and brain (Huang 1999; Pandey et al. 2005)
	Fatty infiltration in the hepatic tissue producing steatosis (Shil and Pal 2017a)
	Enhanced accumulation of chromium in the kidney of mice and muscle of aquatic organism (Shil and Pal 2017b; Loumbourdis et al. 2007)

findings (Soudani et al. 2011). Decreased HDL cholesterol in Cr(VI) toxicity indicates impaired reverse cholesterol transport from blood to the liver which is thought to promote the development of atherosclerosis probably due to lack of defensive effect of HDL to decrease oxidation of other lipoproteins. The increased triglyceride level in serum may be due to increased synthesis of fatty acids in the liver to meet the demand of energy in case of glucose- and protein-deprived situation imposed by Cr (VI). This is supported by the fact that Cr(VI) toxicity is found to stimulate the activity of fatty acid synthase that may contribute to excess accumulation of fatty acids in hepatic tissue resulting in enhancement of lipid synthetic machinery. All these metabolic dysfunctions imposed by chromium have significant impact on metabolic homeostasis that can lead to functional disorder in different organs.

Summary

Environmental pollutants are the major cause of serious health complications. People are exposed to those pollutants from different sources like air, water, soil, industries, foods, etc. Certain metals, heavy metals, and metalloids behave as toxic elements when these are contaminating atmosphere and simultaneously produce adverse effects on plant and animal kingdom. Chromium, being a heavy metal, is found to have some impact on human health. As a trace element, the trivalent chromium is needed for function of specific enzymes of carbohydrate and fat metabolism in human, but the hexavalent chromium due to its easy penetrating ability within cell produces certain effects on cellular metabolism and function. Four major sources of chromium have been identified so far: welding, tanning, chrome plating, and industrial effluents. People engaged in those works are being regularly exposed to chromium compounds and may suffer from some common adverse symptoms like skin irritation and rashes, allergic infection of nasal epithelia, and respiratory distress. However, common man may get exposed to this noxious element mainly through food chain and drinking water contaminated with

chromium. Deposition of chromium within body over the time disturbs normal physiological attribution via alteration of certain parameters of cellular metabolism and bioenergetics.

Morphophysiological alteration by hexavalent chromium has been documented in mice model for short-term exposure. Fatty inflammation along with steatosis due to overaccumulation of Cr(VI) in the hepatic tissue is one of the remarkable adverse changes of hexavalent chromium in mice model. In intracellular compartment, Cr(VI) imposes excess production of free radicals and different stress molecules which may lead to form cellular hypertrophy resulting in mild moderation of the organo-somatic indexes among the liver and kidney. The observations revealed earlier illustrate that carbohydrate, protein, and fat metabolic profiles in the liver, kidney, and blood are severely affected by hexavalent chromium exposure. Hypoglycemia is one of the prominent features of Cr(VI) toxicity as evidenced from the earlier study. This might be due to renal glycosuria or impaired nephritic absorption of glucose with altered morphophysiology of the renal tissue. Plunging of muscle and liver glycogen and pyruvate content assures enhancement of glycogen breakdown as well as exhaustion of carbohydrate metabolites from the affected tissue. Decreasing trend of pyruvate indicates retardation of the glycolysis in all the Cr(VI)-exposed tissues. Altered activities of LDH in the hepatic tissue describes the toxic manifestation of Cr(VI) owing to reduced glycolysis with the less production of pyruvate. Increased LDH activity in the renal tissue promotes anaerobic conversion of pyruvate to lactate which may contribute to energy deficit from carbohydrate source.

Cr(VI) employs considerable effect on cellular energy generation in different organs including the liver and kidney through domination on the vital metabolic processes like TCA cycle and gluconeogenesis and also by altering protease and oxidative phosphorylation enzymes. It significantly altered intermediatory by-products of various metabolic pathways and seriously hampered the normal physiochemical attribution of specific cell. Moreover, Cr(VI)-induced alteration of proteases in the abovementioned tissue may be either due to depletion of specific substrates or due to changed structural conformity of the enzymatic protein by the toxicant. Lipid profile among the experimental organism was drastically changed that showed a derogative expression in terms of altered fat metabolites and accessory parameters such as LDL, HDL, cholesterol, and triglycerides. To compensate energy deficiency in the hepatic tissue, the fatty acid synthesis was triggered by the fatty acid synthase enzyme and enhanced lipogenesis as indicated by increased IDH activity in that tissue as well as overproduction of cholesterol and triglycerides in serum samples of mice after chromium exposure. In response to these, the reverse transport of cholesterol from blood to the liver was hampered due to less production of HDL cholesterol in Cr(VI) toxicity.

Overall it is suggested that Cr(VI) exclusively deteriorates cellular energy generation; collapses homeostatic interrelation of carbohydrate, protein, and fat metabolic pathways; deregulates metabolically linked enzymes; and seriously hampers the structural and functional integrity of the liver and kidney that are supposed to be responsible for their functional imbalance in response to excess chromium exposure (Shil and Pal 2017a, b).

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