

Chromium, its properties, transformation, and impact on humans

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This review presents current views on the features of chromium and its compounds, their interconversion, reduction of Cr (VI) by microorganisms, as well as the impact of chromium (VI) on the environment and humans. Chromium can have positive and negative effects on health, according to the dose, exposure time, and oxidation state. The most common forms of this metal in biological systems are trivalent Cr(III) and hexavalent Cr(VI). Hexavalent chromium is mobile, highly toxic to humans, and animals and considered a priority environmental pollutant. He is highly soluble and mobile. On the contrary, Cr(III) has relatively low toxicity and mobility and it is one of the micronutrients needed by humans. Chromium (III) is an essential nutrient required to promote the action of insulin in body tissues so that the body can use sugars, proteins, and fats. Considerable attention is paid to the issues of interconversion of chromium compounds, reduction of Cr (VI) to Cr (III) by microorganisms, as well as physiological features of their action in humans. The present review discusses on the types of chromate reductases found in different bacteria, their mode of action, and potential applications in the bioremediation of hexavalent chromium. In the human body chromium (VI) is rapidly reduced to chromium (III) after penetration of biological membranes and in the gastric environment. The reduction of Cr(VI) to Cr(III) results in the formation of reactive intermediates that together with stress oxidative tissue damage and a cascade of cellular events, contribute to the cytotoxicity, genotoxicity, and carcinogenicity of Cr(VI)-containing compounds.

Key words: chromium; genotoxicity; carcinogenicity; reduction Cr(VI); organism; intoxication.

INTRODUCTION

The distribution of metals in the environment is related not only to their concentration but also to their bioavailability [1]. Chromium is a naturally occurring element found in animals, plants, soil, and volcanic dust and gases. Chromium has oxidation states (or “valence states”) ranging from chromium(-II) to chromium (VI) [2]. Chromium is the 7th most abundant element on the Earth and the 21st on the Earth’s crust (0.1–0.3 mg kg⁻¹) [3]. The most common forms of this metal in the environment and in biological systems are the trivalent Cr(III) and hexavalent Cr(VI) [4]. Other intermediate valence states of Cr exist in nature, but they are generally unstable.

Cr(III) is scarcely mobile and low bioavailable, and is naturally present in insoluble

inorganic compounds at pH < 4; as the pH increases, Cr(III) is more present in hydrolyzed forms, which are anyway not very soluble and tend to bind organic substances [2, 5]. On the contrary, Cr(VI) is very mobile because it forms soluble inorganic compounds like chromates (CrO₄²⁻) or dichromates (Cr₂O₇²⁻) oxyanions, compounds that are extremely toxic and carcinogenic to all living organisms [4, 6, 7]. Cr (III) is the most stable form in biological systems [8] it does not penetrate biological membranes easily, and it appears that the transport of specific chromium compounds is strictly regulated by the organism. Cr (III) ion has a strong tendency to form coordination compounds with a very slow reaction rate. Chromium (III) shortage can cause cardiac problems, metabolic dysfunctions, and diabetes [9]. Because the body’s ability to

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control blood glucose is critical to many life functions, a consequence of Cr supplementation can be improved health and life span [10]. The biological function of chromium (III) is not fully known yet. It is postulated that chromium affects thyroid metabolism in humans. The binding of Cr (III) with nucleic acids has been found to stimulate DNA-dependant RNA synthesis. Also interaction of Cr (III) is with the hormone insulin and its receptors. This suggests that Cr (III) acts with insulin on the first step in the metabolism of sugar entry into the cell, and facilitates the interaction of insulin with its receptor on the cell surface [11]. Chromium (III) compounds have a relatively low order of toxicity when ingested.

Public concerns with chromium are primarily related to hexavalent compounds owing to their toxic effects on humans, animals, and microorganisms. Chromium (VI) is a potentially toxic metal occurring in water and groundwater as a result of natural and anthropogenic sources. Risks for human health range from skin irritation to DNA damage and cancer development, depending on dose, exposure level, and duration [12]. The high toxicity of Cr(VI) is attributed to its strong oxidizing effect on the intracellular proteins and nucleic acids since hexavalent chromium compounds have high solubility and permeability of cell membrane [13].

PROPERTIES AND TRANSFORMATION OF CHROMIUM COMPOUNDS

It is thought that Cr(VI) is carcinogenic while Cr(III) has such low toxicity that deleterious effects from excessive intake of this form do not occur readily. It becomes toxic only in extremely high amounts. For example, cats tolerate 1000 μg Cr(III)/day and rats 100 μg Cr(III)/kg b.w. [11].

Hexavalent Cr is more soluble than trivalent Cr and at least five times as toxic [14]. The safety limit for Cr³⁺ is approximately 1:10 000. Cr³⁺ toxicity is in fact lower than the toxicity of all other essential elements such as Cu, I₂, Zn, Mn, and especially Se [15]. The toxicity of

Cr⁶⁺ compounds is most probably based on an oxidative DNA impairment [16]. It is assumed that genotoxicity may be due to a transient form (Cr⁵⁺) of intracellular origin formed by the reduction of Cr⁶⁺ to Cr³⁺ [17]. Extracellular reduction of Cr⁶⁺ to Cr³⁺ is regarded as a protective reaction [18, 19]. In addition, it is difficult to distinguish between the effects caused by chromium (VI) and those caused by chromium (III) since chromium (VI) is rapidly reduced to chromium (III) after penetration of biological membranes and in the gastric environment [2, 20, 21].

The evaluation of toxicity of Cr³⁺ supplements has revolved around questions of genotoxicity, mutagenicity, and cancer for several reasons. First, carcinogenic Cr⁶⁺ is metabolized to Cr³⁺ in the body, and Cr³⁺ may be one of the ultimate species that interacts with DNA in Cr⁶⁺-induced cancers [22]. Second, the chemistry and bioavailability of Cr³⁺ are altered by its coordinating ligands.

The trivalent chromium, however, exists mainly as chromium oxide (Cr₂O₃) or chromium hydroxide (Cr(OH)₃); both species have low solubility and are biologically unavailable. Cr(III) can also be oxidized to Cr(VI) in the presence of oxygen and manganese oxides. It has been reported that manganese oxides mediate the transfer of electrons between Cr(III) and the oxygen that is in air and that the amount of Cr(III) oxidized to Cr(VI) is proportional to the reduction rate of manganese [23]. Oxidation of Cr(III) by manganese oxides is controlled by the surface characteristics of the oxides and Cr(III) concentration.

However, chromium is the same as any other mineral element in that its high dose is the poison. The question that remains to be determined is the concentration at which the various forms of orally ingested chromium become toxic because homeostatic mechanisms are unable to prevent chromium accumulation in high enough quantity in cells that will allow chemical reactions that can cause non-repairable damage.

REDUCTION OF Cr(VI) BY MICROORGANISMS

Several different microorganisms have adopted various strategies to counter-effect the toxicity of Cr(VI). Among different methods, enzymatic reduction of Cr(VI) into Cr(III) by microorganisms is the best characterized mechanism for its bioremediation [7, 24]. All Cr(VI)-resistant microbes cannot reduce Cr(VI). However, Cr(VI) resistance is a common phenomenon in all Cr(VI) bioreducers, which delivers proficiency in detoxification process [24]. The catalysis of Cr(VI) reduction can be demonstrated using chromosome or plasmid-encoded non-specific enzymes [25-27]. These enzymes are mainly oxidoreductases such as chromate reductases (ChrA and YieF), NADH-dependent nitroreductase, iron reductase, quinone reductases, hydrogenases, NADH/NADPH-dependent flavin reductases, and NADPH-dependent reductases [28-30]. Even many microorganisms exhibited Cr(VI) reduction using reductases with multiple substrate specificity. Cr(VI) reduction enzymes have shown inductive or constitutive expression in different microorganisms [31, 32].

Biological Cr(VI) reduction activities can occur at extracellular, cell membrane, and intracellular locations in aerobic and anaerobic conditions [25, 33]. Extracellular Cr(VI) reduction is regulated by soluble (cytoplasmic) proteins exported to the extracellular medium by an energy-intensive process [34-36]. This mechanism protects microbes from the harmful effects of Cr(VI) by minimizing its active intracellular transport [37]. In anaerobic reduction, microorganisms may use Cr(VI) as the terminal electron acceptor in an electron transport system associated with membrane-enclosed regions [38]. Consecutively, the transformation of Cr(VI) into Cr(III) can also occur spontaneously in microorganisms by chemical reactions using different intracellular or extracellular compounds, metabolic end products, and intracellular reductants of ascorbate glutathione, cysteine, and hydrogen peroxide (H₂O₂) [39-42].

The enzymatic reduction of Cr(VI) to Cr(III) can also yield variable concentrations of ROS, which may or may not involve the formation of reactive intermediates [27, 43, 44]. However, different reductase enzymatic activities have some ability to alleviate the effects of ROS.

Different chromate reductases such as ChrR, YieF, NemA, and LpDH, have been identified from bacterial sources which are located either in soluble fractions (cytoplasm) or bound to the membrane of the bacterial cell. The reducing conditions under which these enzymes are functional can either be aerobic or anaerobic or sometimes both. Enzymatic reduction of Cr(VI) to Cr(III) involves the transfer of electrons from electron donors like NAD(P)H to Cr(VI) and simultaneous generation of reactive oxygen species (ROS) [7].

Chromate reduction via chromium reductase (ChrR) is a key strategy for detoxifying Cr(VI) to trivalent species of no toxicity. In a study [45], ten bacterial isolates were isolated from heavily polluted soils, with a strain assigned as FACU (chromium-resistant *Escherichia coli*), being the most efficient one able to reduce Cr(VI). FACU was identified as *Escherichia coli* based on morphological and 16S rRNA sequence analyses. Growth parameters and enzymatic actions of FACU were tested under different experimental conditions, in the presence of toxic chromium species. The *E. coli* FACU was able to reduce chromate at 100 µg/mL conceivably by reducing Cr(VI) into the less harmful Cr(III). The results support that FACU is a promising source of ChrR capable of bioremediation of toxic chromium species [45].

Elevated Cr(VI) concentrations can reduce the abundance of microbial communities by electron competing ability, inhibition of extracellular polymeric substances synthesis, and other effects including overproduction of ROS, protein and enzyme dysfunction, destruction of thiol and iron-sulfide cluster, inhibition of functional genes, nutrient assimilation and metabolic pathways, lipid peroxidation, DNA damage, etc. [46-48].

The role of chemicals beyond electron donors and mediators for improved Cr(VI) reduction also exists. For example, heavy metals such as Cu(II), As(III), and Fe(III) that acted as shuttles to accelerate Cr(VI) reduction activity has also upgraded reduction performance by some other effects. Some bacteria use Cu as a protective agent for oxygen-sensitive chromate reductase in Cr(VI) reduction [31]. This metal was also reported to trigger a Cr(VI) reducing enzyme, NAD(P)H-flavin oxidoreductase (NfoR), by acting as a ligand and changing the enzyme conformation [49]. In a different study, the employment of CuO nanoparticles on a biological system activated multiple redox enzymes, and sulfur- and nitrogen-containing proteins for the positive effects on Cr(VI) bioreduction [50]. A Cu-dependent Cr(VI) reductase is also evident in a bacterium, *Amphibacillus* sp. KSUCr₃ [31].

EFFECTS OF CHROMIUM (VI) ON THE ENVIRONMENT AND HUMANS

Among heavy metals, chromium is regarded as an important pollutant environment [51]. Contamination of soils and groundwater caused by the use of this metal in various anthropic activities is a worldwide problem that has been studied by the scientific community for decades [1].

Most Cr(VI) compounds are man-made and human-caused Cr(VI) contamination is a result of large industrial emissions, mainly from metallurgical, chemical, and refractory brick industries [12, 52, 53]. All these activities have contributed to a significant increase in Cr concentration in the environment. The leather and tannery industries, in particular, are the most responsible for the stream of this metal into the biosphere [54], despite many efforts that have been made during the last years to limit the risks of contamination and improve the quality of effluents deriving from these activities. Chromium basic sulfate (Cr₂(OH)(SO₄)₃) is mainly used to tan leather; it oxidizes the organic materials of the hide,

reducing and precipitating inside the tissue as Cr₂O₃ or Cr(OH)₃ compounds, which soften the leather and work as mordant for the subsequent coloring process [55].

The International Agency for Research on Cancer (IARC) has determined that chromium (VI) compounds are carcinogenic to humans [56]. Chromium enters the body through the lungs, gastrointestinal tract, and to a lesser extent through the skin. Inhalation is the most important route for occupational exposure, whereas non-occupational exposure occurs via ingestion of chromium-containing food and water. However, the EFSA Panel on Contaminants in the Food Chain noted that the contribution of drinking water to total Cr refers to Cr(VI), whereas in food the trivalent form Cr(III) is the major form. Mean chronic exposure assessment for Cr(VI) across European dietary surveys through the consumption of drinking water ranged from 0.7 ng/kg b.w. per day to 159.1 ng/kg b.w. per day [57].

It should be noted that the absorption of Cr(VI) is poorer by the oral route, it is thus not very toxic when introduced by the oral route. But chromium is very toxic by dermal and inhalation routes and causes lung cancer, nasal irritation, nasal ulcer, hypersensitivity reactions, and contact dermatitis [58, 59].

The first defense against chromium (VI) after oral exposure is the reduction of chromium (VI) to chromium (III) in the gastric environment where gastric juice and ascorbate [61] play important roles by an NADPH-dependent mechanism [60, 61].

The bioreduction can be carried out under aerobic and anaerobic conditions. Under the anaerobic conditions, glutathione, amino acids, vitamins, etc., act as electron donors, which require NADH/NADPH as cofactors, and the activity soluble reductase can transfer electrons to Cr(VI) which accepts electrons to be reduced; under the aerobic conditions, soluble reductase helps reduce Cr(VI) to insoluble Cr(III) [62].

Inhaled Cr(VI) enters the respiratory system, where it may remain, be reduced, or

enter the bloodstream. It has been suggested that chromium concentrations in human lungs increase with age [63]. Absorption by inhalation exposure appears to occur rapidly for water-soluble chromium (VI) compounds. Chromium (III) is retained to a greater extent in the lungs than is chromium (VI) [64]. Cr(VI) may be reduced to Cr(III) in the lungs or plasma and excreted as Cr(III) in the urine. Cr(VI) that is not reduced in the plasma may enter erythrocytes and lymphocytes [11].

The reduction of chromium (VI) in the red blood cell occurs by the action of glutathione. Since the red blood cell membrane is permeable to chromium (VI) but not chromium (III), the chromium (III) formed by the reduction of chromium (VI) by glutathione is essentially trapped within the red blood cell. The formed chromium-hemoglobin complex is stable and remains sequestered within the cell over the lifespan of the erythrocyte. Eventually, the diffusion of chromium(VI), the reduction to chromium(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane. Thus, there is a physiological drag so that increased diffusion results in greater chromium concentrations in the cell [63]. It appears that the rate of uptake of chromium(VI) by red blood cells may not exceed the rate at which they reduce chromium(VI) to chromium(III) [65].

Chromium transported by the blood is distributed to other organs, the most significant retention being found in the spleen, liver, and bone marrow [66, 67]. Cr intoxication is characterized by pathological anatomical changes in the kidneys and liver. Acute intoxication with Cr⁶⁺ leads to acute renal tubular necrosis characterized by significant interstitial change and subsequent renal failure [68]. Renal glomeruli usually remain intact. The hepatic parenchyma develops necrosis only at very high Cr⁶⁺ doses. The main routes for the excretion of chromium are via kidney /urine and the bile feces [58, 69]. The remaining chromium is deposited into deep

body compartments, such as bone and soft tissue.

Currently, Cr exposure is associated with a variety of diseases, from dermal exposure, which induces a hapten sensitization via an inflammasome activation mechanism, to carcinogenicity with various forms of exposure and mechanisms, including genomic instability or epigenetic alterations [70-72] and respiratory, hepatic, renal, and reproductive problems, and neurological disorders [56].

In reality, Cr(VI) toxic actions come from complex physiological processes that involve multiple routes and interactions with a large number of biological molecules, including proteins, nucleic acids and DNA [73]. Many of those biological macromolecules present polymorphisms with distinct individual physicochemical and dynamic characteristics, making one organism different from another and with unique behavior.

THE MECHANISM OF BIOLOGICAL ACTION OF CHROMIUM

After absorption Cr(VI) readily penetrates cell membranes. Cr(VI) uptake appears to be a combination of saturable transport and passive diffusion. The same anion carrier protein, called band 3 anion transport protein (also known as anion exchanger 1 [AE1]), also transports chromate, sulfate, and phosphate ions through the anion channels [74]. Cr(III) is unable to enter the cells but Cr(VI) enters through membrane anionic transporters. The reaction with genetic material is the basis for the carcinogenicity of some Cr (VI) salts. Cr (VI) is a strong oxidant - in the form of chromates and dichromates it penetrates biological membranes and reacts with cell contents, proteins, or nucleic acids while being reduced to Cr (III). Intracellular Cr(VI) is metabolically reduced to Cr(III). Cr(VI) does not react with macromolecules such as DNA, RNA, proteins and lipids [73, 75].

The details of Cr(VI) toxic activity assumed that genotoxicity, including a wide variety of effects such as DNA damage, gene mutation, sister chromatid exchange, chromosomal

aberrations, cell transformation, and dominant lethal mutations, may be due to the reduced forms of intracellular origin, formed by the reduction of Cr(VI) to Cr(III) [17].

However, both Cr(III) and the reductional intermediate Cr(V) are capable of coordinate, covalent interactions with macro-molecules. Due to its low membrane permeability, Cr(III) can be accumulated within the cells up to several hundred times, creating a high chemical potential for intracellular reactions that involve this species [70]. In addition, it can induce morphological alterations of the membrane, disrupt cellular functions and integrity, and finally cause DNA damage [71]. In fact, Cr-DNA complexes tend to occur preferentially in the nuclear matrix, where diverse processes occur, including DNA replication, transcription, and RNA processing [76].

But high doses of chromium and long-term exposure to it can give rise to various, cytotoxic and genotoxic reactions. A series of *in vitro* and *in vivo* studies have demonstrated that Cr(VI) induces oxidative stress through enhanced production of reactive oxygen species (ROS) leading to genomic DNA damage and oxidative deterioration of lipids and proteins [73, 77]. A cascade of cellular events occurs following Cr(VI)-induced oxidative stress including enhanced production of superoxide anion and hydroxyl radicals, increased lipid peroxidation and genomic DNA fragmentation, modulation of intracellular oxidized states, activation of protein kinase C, apoptotic cell death and altered gene expression [78]. Some of the factors in determining the biological outcome of chromium exposure include the bioavailability, solubility of chromium compounds and chemical speciation, intracellular reduction, and interaction with DNA. The chromium genotoxicity manifests as several types of DNA lesions, gene mutations, and inhibition of macromolecular synthesis. Further, chromium exposure may lead to apoptosis, premature terminal growth arrest, or neoplastic transformation. Chromium-induced tumor suppressor gene p53 and oxidative

processes are some of the major factors that may determine the cellular outcome [58].

CONCLUSIONS

A review is presented, which summarizes the material on the biological action of chromium compounds, and their transformation in humans and microorganisms. Trivalent chromium has relatively low toxicity, while hexavalent chromium is highly toxic to humans and is considered a dangerous pollutant. High doses of chromium and long-term exposure to it can give rise to various cytotoxic and genotoxic reactions in the human body. The high oxidative potential of Cr (VI) causes oxidative stress due to the increased production of reactive oxygen species, which leads to damage to genomic DNA and oxidative damage to lipids and proteins.

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ХРОМ, ЙОГО ВЛАСТИВОСТІ, ТРАНС-ФОРМАЦІЯ ТА ВПЛИВ НА ЛЮДИНУ

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В огляді представлено сучасні погляди на особливості хрому та його сполук, їх взаємоперетворення, відновлення Cr(VI) мікроорганізмами, а також вплив хрому (VI) на навколишнє середовище і здоров'я людини залежно від дози, тривалості дії та ступеня окиснення. Найбільш поширеними формами цього елемента в біологічних системах є три- та шестивалентний хром. Останній є найбільш токсичним, високотоксичним для людей і тварин, вважається пріоритетним забруднювачем навколишнього середовища. Він добре розчиняється. Тривалентний хром, навпаки, має відносно низьку токсичність та рухливість. Він є есенціальним елементом, який необхідний для підсилення дії інсуліну в тканинах організму, для засвоєння вуглеводів,

білків та жирів. Значну увагу приділено питанням взаємоперетворення сполук хрому, відновленню Cr(VI) у Cr(III) мікроорганізмами, а також фізіологічним особливостям їх дії в організмі людини. У цьому огляді розглядаються типи хромат-редуктаз, що містяться у різних бактеріях, спосіб їх дії та потенційне застосування в біоремедіації шестивалентного хрому. В організмі людини останній швидко відновлюється до Cr(III) після проникнення через біологічні мембрани або в шлунковому середовищі. Таке відновлення призводить до утворення реакційно здатних проміжних сполук, які разом із стрес-оксидативним пошкодженням тканин та каскадом клітинних реакцій, сприяють цитотоксичності, генотоксичності та канцерогенності Cr(VI)-вмісних сполук.

Ключові слова: хром; генотоксичність; канцерогенність; відновлення; організм; інтоксикація.

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