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A study of the biotransformation of copper and chromium inside a mammalian liver

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Abstract

Copper and chromium both have been observed to pose a threat to the liver as with increase in concentration as revealed by an increase in the activity of enzymes, the biomarkers of the liver functions like alkaline phosphatase, transaminase, lipid peroxidase, glutathione-s-tranferases and decrease in activity of ATPase in various related studies. The facts are further supported by altered histo-pathological changes.

Keywords: Copper, chromium, biotransformation, metabolism, mammal, liver

Introduction

Copper and chromium, both are trace heavy metals. On being absorbed by the intestine, these metals pass on to the liver via portal vein. The absorption of copper and chromium by the intestine involves the important chaperones like ATP7A (Lutensko and Petris, 2003). The copper in the cupric form (Cu^{2+}) received by the liver is then changed to the cuprous form (Cu^{+}) in the presence of glutathione. The cuprous form triggers many cellular processes. Copper is either used for the formation of ceruloplasmin by the trans-golgi network or transported via vesicles with ATPase for the possible secretion via bile to the intestine (Wapnir, 1998). Simultaneously it also attaches itself to transcription factor complex which stimulates the 5' metal regulatory elements (MRE) arranged in tandem repeat that stimulates the synthesis of apo-metalothioneins which binds with copper(I) to form copper metalothionein.

Copper is either sequestered with metallothioneins to get eliminated from the liver via the biliary secretion or with lysosomes loaded with ATP7A and Ctr1 that are known metallo-chaperones for the transport of copper (Pena *et al.*, 1999; Prohoska, 2004; Knopfel *et al.*, 2005). However these transporters are known to regulate cellular pharmacology and sensitivity (Safaei and Howell, 2005).

The observations in the present investigation show subsequent increase in metallothioneins under stress of copper with increase in lipid peroxidase activity, which is correlated with decrease in the activity of ATPase. It is suggestive that copper gets sequestered inside the liver with metallothionein (Coyle *et al.* 2002). However, the quantity of copper reaching the liver was large enough that led to degradation of the liver as revealed in the histopathological study of the

liver and increase in the activity of alkaline phosphatase, transaminase and lipid peroxidase also. Hence its excretion has also been possible via biliary excretion as demonstrated by increase in the activity of glutathione-s-transferase.

Chromium gives more pronounced effects as compared to copper, which is confirmed by the study of median lethal dose, toxicity induced biochemical parameters in the liver and serum and histopathological details. However, action of chromium is dependent on its oxidation state i.e. only one form, chromium (VI) gets transported by means of transporters in the membrane of small intestine, since it forms tetrahedral complexes (Gomes et al., 2005).
As observed in the present investigation chromium induced the formation of metallothioneins, increased glutathionine-s-transferase inside the liver and alkaline phospahatase, transaminases and lipid peroxidation activity with reduction in the activity of ATPase in the liver as well as the serum. Once it gets reduced to chromium (III), in the presence of glutathione, cytochrome P450, probably is secreted via biliary pathways and kidneys (Anderson and Kozlovsky, 1985; Tiwari and Saxena, 2017; Tiwari et al., 2019, Tiwari et al., 2020; Tiwari et al., 2020; Tiwari et al., 2020).

Detoxification pathways of copper and chromium

The transition metals such as copper, chromium, molybdenum and zinc are essential for life because of the catalytic and structural roles that they play in proteins and other biomolecules. Excessive concentration of essential as well as non-essential metal ions like cadmium, mercury and lead can induce toxicities at the cellular, tissue and organ level.

Mechanism of detoxification

Most organisms utilize a redundant array of selection of cellular mechanisms that are utilized by mammalian cells to detoxify metals, which fall under the scope of systems that can be subdivided into:

a. Mechanism to reduce metal uptake.

The reduction of metal importation to limit toxicity can operate through inhibition of import machinery for the metal or by making the extracellular metal unavailable for absorption. For example, the level of iron taken up by the mammalian cells is primarily regulated by, controlling at a transitional level, the membrane concentration of the receptor for the iron transport protein ferritin (Vincent, 2000). Similarly, action of chromium independent on the binding of insulin with its receptors and glucose tolerance factor, which acts as chromium binding substance (Davies, 1985).

b. Enhance metal sequestration

The intracellular chelation or sequestration of metals into relatively innocuous complexes or organelles is a commonly used mechanism to limit their toxicity. In many cases, the chelating agents are peptides or proteins that form stable complexes, which limit the reactivity or help in its excretion (Yuann *et al.*, 1999). In addition to providing a means of limiting the reactivity and toxicity of essential metals, some complexes appear to serve as storage sites for the metal ions. The metal or metal complexes sequestration process is an initial step towards their export or they may be pumped into a vesicle for storage or extrusion by vesicle.

c. Export

Export of metal ions to limit their toxicity within the cell is a ubiquitous process. The cation transporting P-type ATPase is among the most common pumping mechanisms used to transport metal ions out of cells or into the organelles. The basic pump design is conserved in all life forms and is used for a range of elements, drugs, toxins and proteins. The sequence, presumably the structure, is frequently modified to increase the specificity and efficacy for a given element. In addition to the ATPase pumps some mammalian cells transport transition metals ions, like zinc by utilizing non-ATPase pumps (Palmiter and Findley, 1995).

d. Redundancy

An essential feature of metal ion detoxification pathways is their redundancy. Many detoxification mechanisms are not entirely specific and are utilized against a number of metal ions.

An example of non-specific detoxification pathway is metallothionein and its function in the sequestration of cadmium, zinc and copper ions (Klassen and Liu, 1998). In conjucation with non-specific detoxification mechanisms, there exist a set of metal ion like copper (voet and Voet, 1993) and chromium (Ye et al., 1999).

e. Metalloregulation

Metalloregulation, broadly defined as a cellular response to an tntracellular metal ion concentration is, well documented in all animal systems, accomplished at transcriptional, translational and enzymatic levels, through metal binding proteins, which serve as conformational switches (O'Halloram, 1993). These proteins allow cells to respond biochemically to increase and decreases in the intracellular copper concentration.

Copper detoxification pathways (Fig. 1)

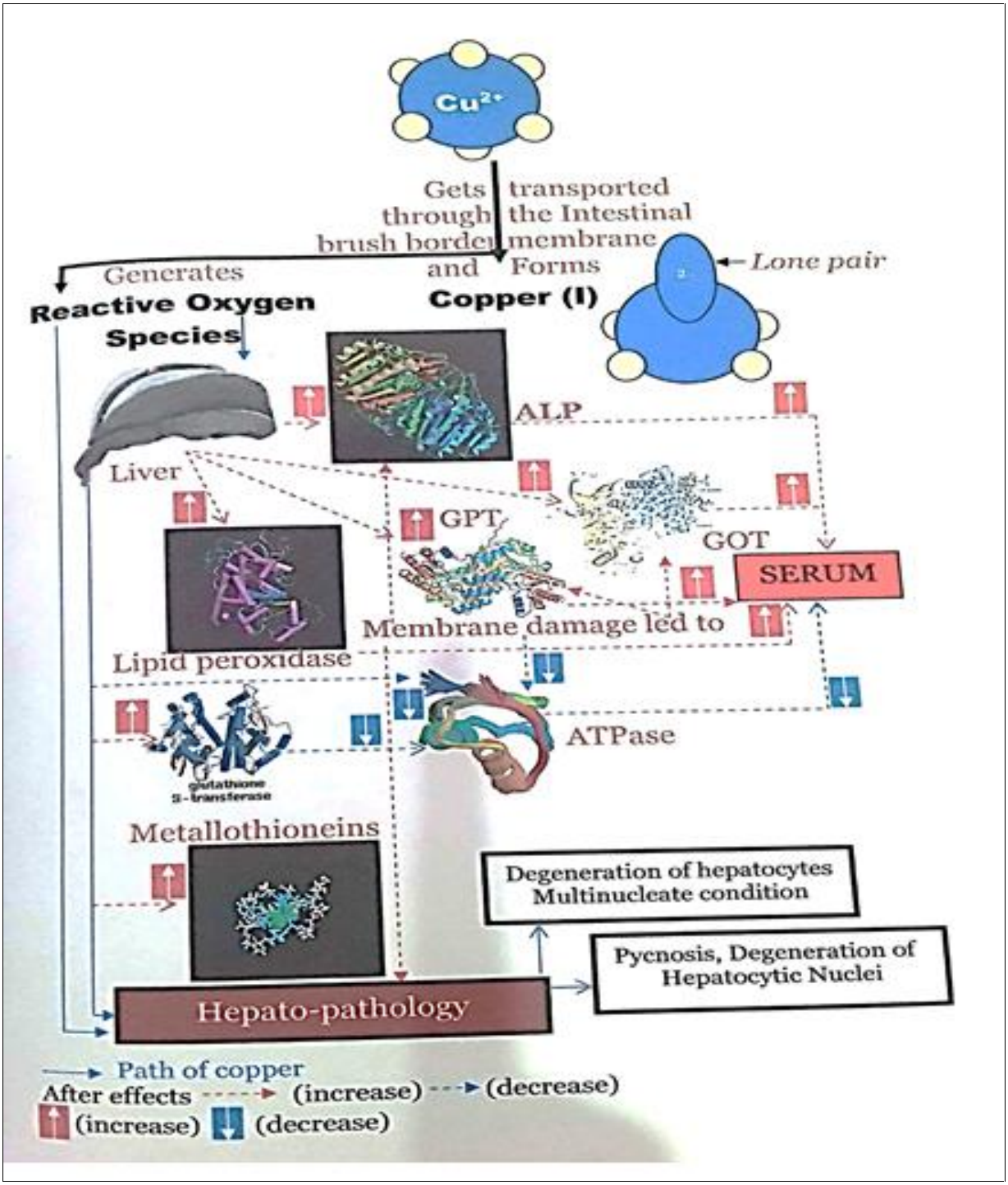

Figure 1: Showing the metabolism of Copper inside the mammalian liver

The mammalian copper detoxification pathways contain at least two mechanisms to detoxify i.e either copper can be sequestered by copper binding proteins, metallothionein into an innocuous complex or excess can be transported out of the cell with the aid of an export pump. Hepatocytes are chosen foe to highlight the pathway because of the liver's central role in the copper metabolism. The mammalian metallothioneins are induced by copper, cadmium, zinc and other transition metals (Hamer, 1986).

All mammalian metallothioneins are homologous, sharing common metal binding motifs, the induction mechanisms. The disruption of the metallothioneins, however, does not lead to marked increase in the copper sensitivity because the cells can use the murine homolog of the Menkes ATPase (Copper ATPase, A P-type family of ATPase) pump to detoxify the excess copper (Payne and Gitlin, 1998; Lutensko and Petris, 2003). However, other transitional metals also can interfere with transport of copper (Chang, 2002).

When copper enters the hepatocytes via blood, after getting being absorbed in the intestine as copper (II), it changes to copper (I) in the presence of glutathione, which helps in the formation of copper transcriptional factor complex, thereby stimulates the promoter region (MRE-Metal Regulatory Element) of the metallothionein gene resulting in formation of Apo-metallothionein which sequesters with copper to form copper metallothioneins. Further, Copper induced metallothionein marked elevation and decrease in the activity of ATPase clearly indicated that the sequestration of copper inside the hepatocytes by metallothioneins, preceded the influx of copper and in the absence of other detoxifying mechanisms such as copper ATPase due to lipid peroxidation of membranes have led to the destruction of hepatocytes and induction of hepatocellular lesions(Tiwari and Saxena, 2017; Tiwari et al., 2019, Tiwari et al.,2020; Tiwari et al., 2020; Tiwari et al., 2020).

Chromium detoxification pathways (Fig. 2)

Chromium detoxification pathways start working soon as it enters the body, since chromium (III) is highly toxic yet cannot cross the brush border membrane of the intestine since it forms octahedral complexes whereas chromium (VI) can readily cross biomembranes and changes to chromium (III) in the presence of ascorbate, glutathione or cytochrome p450 (Kuo et al., 2003) in the saliva and gastric juice or gets sequestered by intestinal bacteria (De Flora, 2000). Moreover, even if chromium (IV) escapes reduction processes, it is absorbed in the intestine, released in the blood of the portal system, and carried to the liver. The blood, particularly RBC has a considerable capacity to sequester and reducing chromium (VI) and liver too can reduce chromium (VI) (Kerger et al., 1996).

Chromium (VI) is absorbed by the intestine and reaches the liver as revealed by the observed variation in the activity of various enzymes and metalloproteins. As far as detoxification is concerned, the detoxification of the chromium does involve the participation of metallothioneins and formation of complexes with enzymes like glutathione-s-transferase as revelaed by increase in the concentration of metallothinein under stress of chromium. As revealed by the histopathology of the liver the degeneration of hepatocytic nuclei has been noted and a mechanism that also is noteworthy for the detoxification via subsequent elimination of chromium from the liver is that chromium (VI) exposed cells can undergo apoptosis as a consequence of DNA damage and undergo subsequent elimination from the organism (De Flora and Wetterhahn, 1989; Bose et al., 1998; Tiwari and Saxena, 2017; Tiwari et al., 2019, Tiwari et al., 2020; Tiwari et al., 2020; Tiwari et al., 2020).

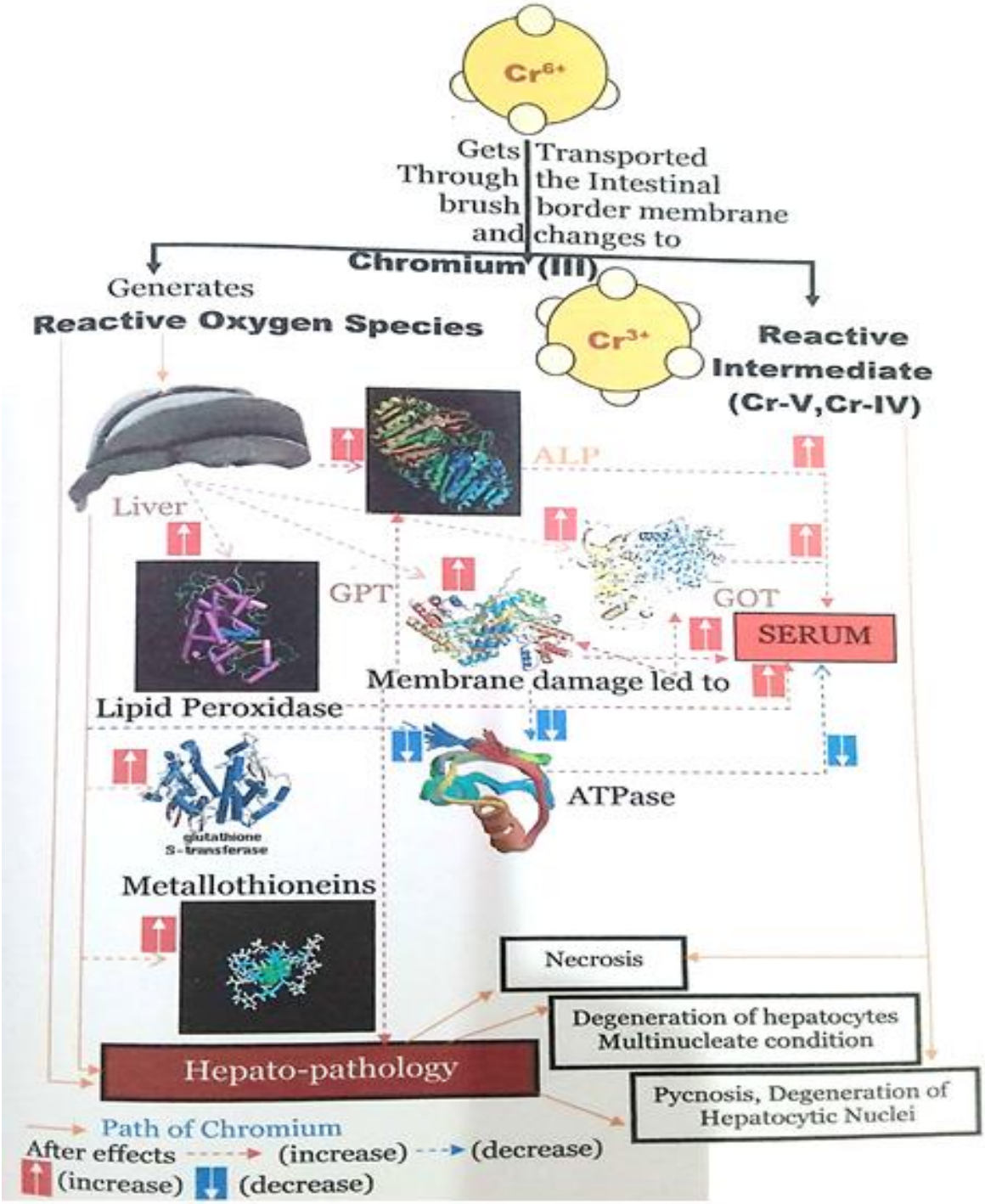

Figure 2: Showing the metabolism of Chromium inside the mammalian liver

Biotransformation potential of copper and chromium

Copper and chromium both have been observed to pose a threat to the liver as with increase in concentration as revealed by an increase in the activity of hepatic and serum enzymes, the biomarkers of liver function like alkaline phosphatase, transmainases, lipid peroxidase, glutathione-s-transferase and decrease in the activity of hepatic and serum ATPase.

Biotransformation potential has been seen to be more in case of chromium as compared to copper since reduction of chromium inside the liver involves generation of reactive oxygen species and reactive intermediates also, which includes oxidative stress leading to genotoxic and carcinogenic effects due to the binding or reactive intermediates and reactive oxygen species with DNA.

The absorption of copper by the intestine occurs where from it passes onto the liver via portal vein. The copper in the cupric form (Cu^{2+}) received by the liver is then changed to the cuprous form (Cu^{+}) in the presence of glutathione generating reactive oxygen species. The cuprous form triggers many cellular processes. Copper is either used for the formation of ceruloplasmin by trans-golgi network or transported via vesicles with ATPase for the possible secretion via bile to the intestine. Simulatenously, it also attaches itself to apo-metallothionein which binds with copper (I) to form copper metallothionein. Chromium gives more pronounced effects as compared to copper, which is confirmed by the study on median lethal dose, toxicity induced biochemical parameters and histopathological details.

Chromium (VI) is absorbed by the intestine and reaches the liver, wherein its reduction results in formation of reactive oxygen species and reactive intermediates such as Cr(IV) and Cr(V), as revealed by the observed variations in the activity various enzymes and metallo-proteins. As revealed by the histopathology of the liver, degeneration of hepatocytes has been noted and a mechanism that also is noteworthy for the detoxification since reactive oxygen species and reactive intermediated such as Cr(V) and Cr(IV) forms covalent compound with DNA or glutathione resulting in apoptosis for subsequent elimination of chromium from the liver and subsequent elimination from the organism.

Once it gets reduced to chromium (III), in the presence of glutathione, cytochrome p450, is secreted primarily via biliary pathways and kidneys (Tiwari and Saxena, 2017; Tiwari et al., 2019, Tiwari et al., 2020; Tiwari et al., 2020; Tiwari et al., 2020).

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