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MEDICINAL APPLICATIONS OF COPPER AND ITS COMPLEXES- A REVIEW

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ABSTRACT

Our desire to understand how the individual molecules that make up cells organize, interact, and communicate to form living systems has led to the burgeoning field of chemical biology, The fundamental role of copper and the recognition of its complexes as important bioactive compounds in vitro and in vivo aroused an ever-increasing interest in these agents as potential drugs for therapeutic intervention in various diseases. The vast array of information available for their bioinorganic properties and mode of action in several biological systems, combined with the new opportunities offered by the flourishing technologies of medicinal chemistry, is creating an exciting scenario for the development of a novel generation of highly active drugs with minimized side effects which could add significantly to the current clinical research and practice. In this paper we attempt to summarize all the available-to-date information on these issues.

KEYWORDS: copper, diseases, therapeutic intervention, medicinal chemistry.

INTRODUCTION

Copper exhibits considerable biochemical action either as an essential trace metal or as a constituent of various exogenously administered compounds in humans. In its former role it is bound to ceruloplasmin, albumin, and other proteins, while in its latter it is bound to ligands of various types forming complexes that interact with biomolecules, mainly proteins and nucleic acids. The multifaceted role of copper in biological systems is demonstrated by several studies. In particular the involvement of copper in human diseases has been described from a medicinal-chemical[1] and a biochemical view[2] focusing on the molecular physiology of Cu transport.[3] Much of the current research effort is cited on copper homeostasis[4] and its relation to iron metabolism[5] as well as the role of copper in biological processes related to

human physiology and pathology.[6,7] While a lot of the functions that have been proposed to account for the homeostasis of inorganic noncomplexed copper in humans have been described[3–5], only a limited number of review studies have focused on the multiple biochemical events which could be directly implicated in the use of copper complexes in medicine.

Current interest in Cu complexes is stemming from their potential use as antimicrobial, antiviral, anti-inflammatory, antitumor agents, enzyme inhibitors, or chemical nucleases. Markedly, the biochemical action of Cu complexes with non-steroidal anti-inflammatory drugs (NSAIDs) has been studied.[8] Numerous Cu(II) complexes of NSAIDs showing enhanced anti-inflammatory and antiulcerogenic activity, as well as reduced gastrointestinal toxicity compared to the uncomplexed drug, have been prepared and structurally characterized.[8] They comprise a class of potential anti-inflammatory drugs with reduced side effects and their mode of action is attributed to their marked superoxide- dismutase- (SOD-)mimetic activity. Other studies have concentrated on the potential chemotherapeutic properties of copper-based compounds.[9,10] Moreover, several authors have brought to attention the antiviral and antibacterial activity of Cu(II) complexes. For instance, it was shown that the infectivity of influenza A virus is reduced after exposure on copper surfaces.[11] The mechanism of this process is only partly understood, but it has been speculated the degradation of the viral nucleic acid takes place after the intervention of copper ions. In addition, the study and development of Cu complexes could be helpful in the design and production of antiviral and antibacterial materials, able to deactivate HIV or H1N1 viruses[12] and antibiotic-resistant bacteria, respectively. Towards this direction, a method of producing copper-impregnated materials that possess broad-spectrum antimicrobial properties has been reported.[13]

Copper Homeostasis

Copper in food (organic copper) is processed by the liver and is transported and sequestered in a safe manner. Inorganic copper, such as that in drinking water and copper supplements, largely bypasses the liver and enters the free copper pool of the blood directly. This copper is potentially toxic because it may penetrate the blood/brain barrier.

About 50% of the average daily dietary copper of around 25 μmol (1.5 mg) is absorbed from the stomach and the small intestine. Absorbed copper is transported to the liver in portal blood bound to albumin and is transmitted to peripheral tissues mainly bound to

ceruloplasmin and to a lesser extent, albumin. The liver contains 10% of the total body content of 1200 μmol (80 mg). Excess copper is excreted in bile into the gut and the faecal copper output (12.5 μmol/24 h) is the sum of unabsorbed dietary copper and that reexcreted into the gut. Cu homeostasis is regulated by alterations in both the absorptive efficiency and biliary excretion in the gut. At low and high intakes, the efficiency of absorption is regulated up and down, respectively, but is predominantly controlled via endogenous excretion.[14]

Copper is incorporated into a number of metalloenzymes involved in hemoglobin formation, drug/xenobiotic metabolism, carbohydrate metabolism, catecholamine biosynthesis and the cross-linking of collagen, elastin and hair keratin as well as in the antioxidant defense mechanism. Moreover, copper-dependent enzymes, such as cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase and dopamine β-monooxygenase, function to reduce reactive oxygen species (ROS) or molecular oxygen.[15] Symptoms associated with copper deficiency in humans include normocytic, hypochromic anemia, leukopenia and osteoporosis. Copper deficiency is rarely observed in the general population.[16]

Oxidative-Stress-Related Disorders

Although copper homeostatic mechanisms play an important role in the prevention of copper toxicity, exposure to excessive levels of copper can result in a number of adverse health effects including liver and kidney damage, anemia, immunotoxicity and developmental toxicity.[17] Many of these effects are consistent with oxidative damage to membranes or macromolecules. Given the capacity of copper to produce large amounts of reactive oxygen species (ROS), an excess of Cu could result in oxidative-stress-related health disorders, many of which can be linked partially to its redox reactivity. Copper has been suggested to facilitate oxidative tissue injury through a free-radical-mediated pathway analogous to the Fenton reaction.[18] By applying the electron spin resonance (ESR) spin-trapping technique, evidence for copper-mediated hydroxyl radical formation in vivo has been obtained.[19-20] ROS are produced through a Fenton-type reaction as follows:

Aceruloplasminemia

Ceruloplasmin is a copper-containing glycoprotein produced in the liver that binds about 95% of the copper in serum. This glycoprotein presents ferroxidase activity and catalyzes the conversion of ferrous to ferric iron which is then transferred to transferrin. A total absence of circulating serum ceruloplasmin (aceruloplasminemia) could lead to ferrous iron abundance

within both the reticuloendothelial system and parenchymal cells.[21] It is noteworthy that hereditary ceruloplasmin deficiency (or aceruloplasminemia) is an autosomal recessive disorder altering iron metabolism. It is accompanied by mutations of the ceruloplasmin (Cp) allele on chromosome 3q.[22] Manifestations of aceruloplasminemia at the clinical level are diabetes mellitus, retinal pigmentary degeneration, dystonia, extrapyramidal signs, cerebellar ataxia and dementia. Histopathologic studies have presented significant agglomeration of iron in the liver, pancreas, retina and central nervous system. Although the pathogenesis of brain damage in aceruloplasminemia is currently not fully understood, it is well recognized that iron-mediated oxidative stress could be implicated in neuronal cell death.[23]

Wilsons disease (WD)

Wilson's disease is an autosomal recessive disease of copper metabolism of which the primary genetic defect is in ATP7B gene.[24] The biological role of ATP7B gene is to encode a copper-transport protein located at the trans-Golgi network and to transfer Cu into the secretory pathway for both annexation into ceruloplasmin and excretion into the bile.[25] A major contribution to pathophysiology of Wilson's disease is Cu-mediated oxidative damage, activation of cell death pathways, and eventual leakage of copper into the plasma pool, which ultimately results in the accumulation of excess copper in extrahepatic tissues. Notably, the hepatic Cu overload associated with WD is histopathologically characterized by bulgy hepatocytes, inflammation and cytoskeletal alterations and finally leads to cirrhosis.[26] WD presents severe neurological symptoms, but when it is diagnosed in time, it can be treated with several ways including the use of chelating agents, low-Cu diets and high levels of Zn supplements.[27]

The Menkes Disease (MD)

The Menkes disease is an X-linked recessive disorder caused by defects in a gene that encodes a copper-transporting ATPase (ATP7A).[28] In humans, the ATP7A gene product functions as an intracellular pump to transport copper into the trans-Golgi network for incorporation into copper-requiring enzymes including dopamine-β-hydroxylase (DBH) and also mediates copper exodus from cells. Copper uptake and excretion by the liver are normal in MD as well as copper enzyme levels, but the absorption of copper in the gastrointestinal tract is severely impaired. The significantly decreased intestinal absorption of copper results in a shortage of exchangeable copper followed by a deficiency of cuproenzymes with important role in the developmental level.[29] It should be emphasized that the uptake by

peripheral tissues is normal; however, excretion and intracellular copper trafficking are disrupted by mutations in the ATP7A gene. As a result of impaired copper efflux, peripheral tissues in MD patients tend to accumulate copper in the form of copper metallothionein. At the clinical level, MD is characterized by progressive neurological impairment and death in infancy. Because of the block in intestinal absorption of copper, the major clinical impact is from copper deficiency in the brain of the developing fetus, leading to severe brain damage.[30]

Alzheimer's disease (AD)

Alzheimer's disease is the most common form of dementia with progressive patterns of cognitive and functional impairments. Increased levels of copper in cerebrospinal fluid accompanied by normal plasma copper concentrations in patients with AD have been found[31], while other researchers have reported elevated free copper plasma levels in AD.[32] In a rabbit model of AD, addition of trace amounts of copper (0.12 ppm) to the drinking water greatly exacerbated the brain AD pathology and loss of cognition.[33] Moreover, a community-based prospective study suggested that high dietary intake of copper in conjunction with a diet high in saturated and trans fats may be associated with accelerated cognitive decline.[34]

Inflammation

Ceruloplasmin acts as an acute-phase reactive protein to stress and trauma conditions. As a consequence, elevated copper concentrations have been found in response to inflammation, infection and various chronic diseases, such as arthritis. Serum copper levels are higher than normal in varied inflammatory diseases in humans.[35] The higher levels of ceruloplasmin are accountable for the increased serum copper in the preceding conditions. Moreover, the anti-inflammatory results of copper have been shown in humans.[36] On the other hand, the acute or chronic inflammation actuates changes on the metabolism of copper, which contribute to altered serum and tissue levels.[37] The increase of serum copper in inflammation could be due to the increase of ceruloplasmin, which is an acute-phase protein. It is well recognized that the role of ceruloplasmin in arthritis is to neutralize free oxygen radicals, mainly anion superoxide, in an attempt to stop the process of turning chronic.[38-39]

Cancer

Increased ceruloplasmin and copper levels in various tissues have been linked to cancer progression.[40] Ceruloplasmin contributes about 90% of serum copper, which is then elevated

secondarily. Moreover, copper deficiency has been evaluated as an anticancer strategy even though clinical studies have not been especially encouraging.[41] While the precise role of copper in cancer development is presently not known, its involvement through ROS production in oxidative stress is possible. Recently, it was shown that copper proteins are associated with metabolic changes in cancer cells[42] and most importantly play a significant role in angiogenesis by stimulating proliferation and migration of human endothelial cells.[43]

Copper Complexes as potential therapeutic agents

Binary Cu(II) Complexes

A number of Cu(II) chelate complexes that exhibit cytotoxic activity through cell apoptosis or enzyme inhibition have been reviewed.[44] Such complexes containing bi-Schiff bases as ligands are effective in reducing tumor size, delaying of metastasis, and significantly increasing the survival of the hosts. Chelates of curcuminoids show significant reduction of solid tumor volume in mice, while complexes of pyridine-2-carbohidrazide derivatives inhibit the expression of c-Src, a nonreceptor tyrosine kinase, which plays a significant role in growth-mediated signaling pathway, thus showing cytotoxicity against colon cancer cell lines. Similarly Cu(II) chelates of salclaldoxime and resorcylaldoxime[45] are potent antiproliferative agents, exhibiting strong cytotoxic effects comparable to that of adriamycin, by inducing cell cycle arrest and apoptosis. Their action may involve the inhibition of the enzyme topoisomerase II activity, by preventing dimer formation of the enzyme and its interaction with DNA.[46] The diverse biological activity of these complexes compared to one of the widely used platinum anticancer drugs cisplatin, indicates different mechanism(s) of action, which have not been yet resolved. It is likely that copper complexes interact with enzymes and inhibit vital cell functions, rather than interact with DNA and induce crosslinks.

Ternary Cu(II) Complexes

Numerous mixed ligand complexes that combine one or two bidentate N,N- and O,O-coordinated ligands have been synthesized and tested for biological activity. Chemical formula of representative Cu(II) ternary complexes together with the coordination mode of various ligands are cited in Table 2. Complexes of the type $[CuLL']^{+}$, where L = N,N-chelate such as phenanthroline or 2,2′-bipyridine and L′ = N,N- or N,O-chelate such as acetylacetonate or glycinate as casiopeinas.[47] They exhibit significant antineoplastic activity in vitro and in vivo, against a variety of tumor cell lines.

CONCLUSIONS

Developing an integrated picture for the role of copper and its complexes in medicine is a challenging task that awaits further exploration. Copper ions are considered as multifunctional participating in a broad spectrum of intracellular processes under normal and pathologic conditions. However, many questions remain unanswered. Further experimental and clinical studies would aid at unraveling their prominent activities, thus discovering effective Cu biomarkers and generating new options for early intervention in copper-related health disorders. Copper complexes described in the present work show a diverse in vitro biological activity, ranging from antibacterial and anti-inflammatory to cytostatic and enzyme inhibitory. At molecular level such complexes interact directly with proteins and DNA, leading to dysfunction and cleavage of the macromolecular structure, or indirectly producing ROS that attack and degrade biomolecules. In conclusion, novel treatment options that interfere with copper complexes have been proposed in experimental systems, albeit their effectiveness in clinical practice remains to be further investigated. The great pressure for producing new effective treatment options in medicine should not surpass the necessity for careful, rationally designed randomized studies evaluating the most promising copper complexes as therapeutic pharmaceuticals.

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