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INVESTIGATION OF THE ROLE OF COPPER ION IN BIOLOGICAL SYSTEMS AND ITS IMPLICATIONS ON DISEASES: A REVIEW

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Abstract

Copper ions are essential for many biological processes, including enzyme function, electron transfer, oxygen transport, and cellular metabolism. Both copper deficiency and excess can lead to severe health complications such as neurodegenerative diseases, cancer, metabolic disorders, and infections. This review explores the critical roles of copper ions in biological systems, emphasizing their interaction with biomolecules and involvement in metalloenzymes like cytochrome c oxidase and superoxide dismutase. Copper's ability to alternate between two oxidation states (Cu(I) and Cu (II)) enables it to facilitate key redox reactions essential for cellular energy production and managing oxidative stress. Dysregulation of copper homeostasis can result in disorders like Wilson's and Menke's diseases, which cause tissue damage and

Introduction

Metal ions are crucial for numerous biological processes, serving as essential components in enzymes and proteins (Chasapis et al., 2020). Many enzymes depend on metal ions as cofactors, which help stabilize their structures and enhance catalytic activity (Rudolf et al., 2018). Iron (Fe), magnesium (Mg), zinc (Zn), and copper (Cu) are frequently involved in catalytic processes, electron transfer, and providing structural support in proteins (Gupta et al., 2020). For instance, metal ions like iron and copper undergo oxidation-reduction cycles in redox reactions, enabling

metabolic disturbances. The review emphasizes the importance of regulating copper levels within the body and highlights the need for further research into copper metabolism to enhance disease prevention and treatment strategies. The insights gained from this review provide a deeper understanding of copper's role in human health and its potential as a therapeutic agent in clinical applications.

Keywords: Copper ION, Metal Ions, Neurodegenerative Diseases, Metabolic Disorders, Infections.

Critical processes such as cellular respiration criticality and photosynthesis (Holzer et al., 2018). Iron plays a central role in oxygen transport through hemoglobin, whereas magnesium ions are vital for ATP stabilization and function in DNA, RNA, and protein synthesis (Petris et al., 2017). Copper is an essential trace mineral critical in various biological functions within the human body (Chasapis et al., 2020). It is integral to several physiological processes, including enzymatic reactions, cellular energy production, and iron metabolism (Gupta et al., 2020; Holzer et al., 2018). Copper ions are crucial for the proper function of several enzymes, including cytochrome c oxidase, which generates ATP through the mitochondrial electron transport chain (Mendez & Rizzo, 2019). Additionally, copper assists in lysyl oxidase activity, an enzyme necessary for the formation and stability of connective tissues by cross-linking collagen and elastin fibers (Adebayo & Akinmoladun, 2020).

Copper is absorbed mainly in the small intestine, where it binds to metallothioneins and chaperone proteins that transport it to various tissues throughout the body. The liver regulates copper levels by storing surplus copper and facilitating its elimination through bile. In the bloodstream, copper is carried by ceruloplasmin, a protein crucial for iron metabolism and antioxidant defense mechanisms (Nwokocha & Asagba, 2022).

Maintaining copper balance is crucial, as deficiencies and excesses can have significant health consequences (Petris et al., 2017; Schaefer et al., 2019). This project aims to explore the diverse roles of copper ions, their impact on health, and potential therapeutic approaches for addressing copper-related disorders (Rudolf et al., 2018). By investigating these aspects, the study seeks better to understand copper's role in health and disease (Tapia et al., 2020; Chasapis et al., 2020).

Role of Metal Ions in Disease

Metal Ions such as copper ions are essential to cellular functions, with their involvement in the disease being critical for several reasons (Holzer et al., 2018; Gupta et al., 2020). Copper is key in redox reactions, iron metabolism, and enzyme regulation (Rudolf et al., 2018; Petris et al., 2017). However, imbalances in copper levels—whether an excess or a deficiency—can lead to severe health conditions, underscoring the importance of studying copper's role in disease for improved prevention, diagnosis, and treatment approaches (Schaefer et al., 2019; Tapia et al., 2020). Copper imbalances are associated with various diseases. For example, in Wilson's disease, excess copper builds up in organs like the liver and brain, causing damage and neurodegeneration (Bandmann et al., 2015). On the other hand, a lack of copper results in Menkes disease, which leads to developmental issues and impaired brain function. Understanding copper metabolism is essential for diagnosing and treating such genetic disorders.

Additionally, copper contributes to the development of cancer and neurodegenerative diseases. Increased copper levels in cancerous tissues promote blood vessel growth, which supports tumor development (Gupte & Mumper, 2009). In neurodegenerative diseases, copper interacts with proteins such as amyloid-beta, accelerating oxidative stress and leading to conditions like Alzheimer's disease (Squitti et al., 2014). Gaining insights into these processes can aid in developing therapies that target copper regulation in cancer and neurodegeneration.

Copper also supports the immune system and helps combat infections. Disruptions in copper balance can weaken the immune response, making individuals more vulnerable to infections. Therefore, understanding copper's role in immune function can help develop treatments for infectious diseases (Gupta et al., 2020).

Copper Ion Homeostasis and Regulation

Homeostasis refers to the process by which biological systems regulate their internal environment to keep conditions stable and optimal for survival, regardless of external fluctuations (Cannon, 1929; Cooper, 2008). This involves feedback mechanisms that control various factors like temperature, pH, hydration, and nutrient levels, ensuring that cells and organs operate effectively (Schmidt-Nielsen, 1997). Copper ion homeostasis is crucial for overall health, as copper is involved in many biological functions (Gupta et al., 2020). It is necessary for enzymatic reactions, maintaining redox balance, and supporting cellular activity (Holzer et al., 2018). However, imbalances in copper levels, whether due to deficiency or excess, can lead to serious health issues, highlighting the importance of effective regulatory mechanisms (Petris et al., 2017; Schaefer et al., 2019). Copper absorption occurs mainly in the small intestine, and the liver plays a pivotal role in regulating copper levels within the

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body. After absorption, copper is transported to the liver, where it is incorporated into ceruloplasmin, a protein that carries copper in the bloodstream. This process helps ensure sufficient copper is available for cellular functions while preventing toxic accumulation (Camakaris et al., 1999).

The body maintains homeostasis through carefully regulated absorption, distribution, and excretion (Petris et al., 2017). Excess copper can be excreted into bile or stored in tissues, particularly the liver and kidneys (Waldron et al., 2017; Schaefer et al., 2019). The regulation of copper levels is managed by proteins such as metallothionein, which binds excess copper to reduce toxicity (Koppula et al., 2018). When these regulatory systems fail, conditions such as Wilson's disease can develop, leading to copper accumulation in tissues, which causes liver damage and neurological and psychiatric symptoms (Bandmann et al., 2015). Copper deficiency can also lead to various health problems, including anemia, osteoporosis, and weakened immune responses. A lack of copper can disrupt the function of essential enzymes like cytochrome c oxidase and superoxide dismutase, which are vital for energy production and protecting against oxidative stress (Harris et al., 2012). In Nigeria, research has underscored the influence of environmental factors on copper homeostasis. For example, Eze et al. (2020) found that elevated copper levels in agricultural soils resulted from using copper-based pesticides, posing health risks to local communities. Similarly, Ofoegbu et al. (2019) discovered high copper concentrations in drinking water sources in certain areas, raising public health concerns.

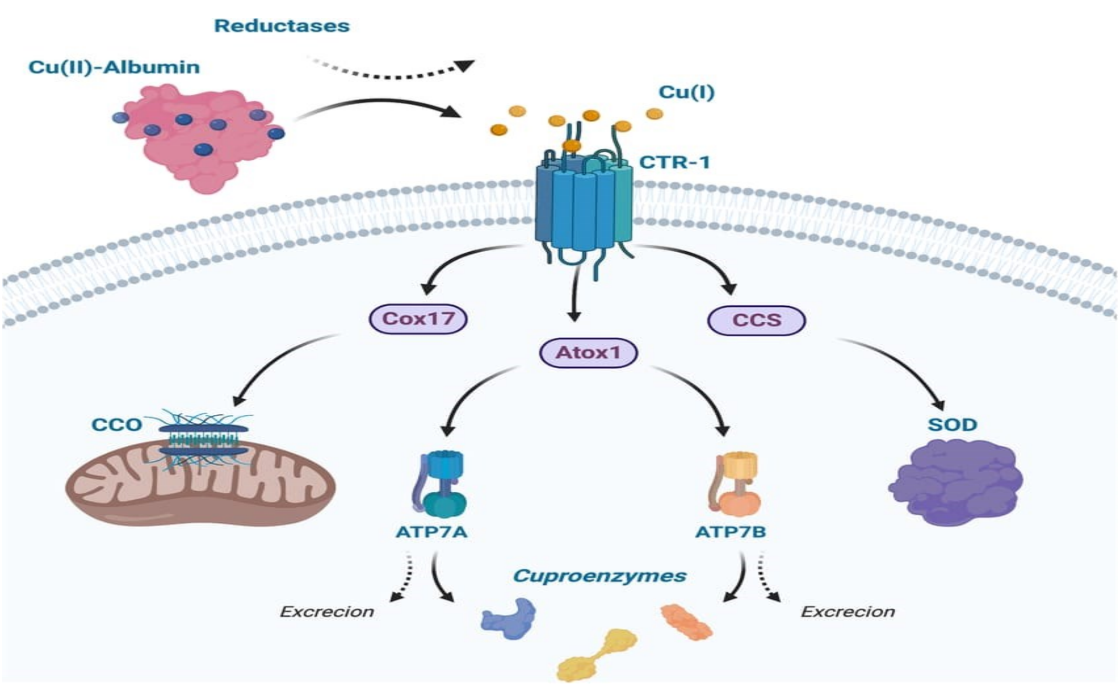

Figure 1.1. Diagram of Copper Ion Homeostasis

Copper Ion in Neurodegenerative Diseases

Copper ions are vital in the development and progression of various neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases (Holzer et al., 2018; Schaefer et al., 2019). Copper is crucial for numerous brain functions, including neurotransmitter synthesis, energy metabolism, and antioxidant defense (Gupta et al., 2020). However, disturbances in copper homeostasis can lead to the onset and advancement of these conditions (Petris et al., 2017). In Alzheimer's disease, research has identified abnormal copper accumulation in the brain. High levels of copper have been associated with the aggregation of amyloid-beta peptides, which form the plaque characteristic of the disease. This accumulation can increase oxidative stress, leading to neuronal damage and cognitive decline (Agnelli et al., 2016).

Additionally, changes in the expression of copper transport proteins like ATP7A and ATP7B may contribute to the dysregulation of copper in Alzheimer's patients (Barker et al., 2017).

Copper imbalance is also a significant factor in Parkinson's disease. Copper is essential for the functioning of dopamine-producing neurons, and studies suggest that elevated copper levels can result in the degeneration of these neurons (Schaefer et al., 2019; Gupta et al., 2020). Specifically, copper accumulation in the substantia nigra, a brain region affected by Parkinson's disease, has been linked to increased oxidative stress and inflammation, exacerbating neurodegeneration (Choi et al., 2019).

The relationship between copper and Huntington's disease is complex. While copper is necessary for normal cellular processes, excessive accumulation can contribute to the toxicity associated with mutant huntingtin protein. Research indicates that copper may influence the aggregation and toxicity of this protein, highlighting the need for strict regulation of copper levels to avoid neuronal damage in Huntington's disease (Huang et al., 2015).

Studies in Nigeria, particularly in areas with environmental contamination, have pointed to heavy metal exposure, including copper, as a significant factor in such diseases (Agbaji et al., 2017). High copper levels have been shown to accelerate amyloid aggregation, which is a hallmark of Alzheimer's progression. Another study by Ugochukwu et al. (2021) found elevated copper levels in the cerebrospinal fluid of Alzheimer's patients, suggesting a potential biomarker for the disease and reinforcing the connection between copper dysregulation and neurodegeneration.

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Copper Ion in Cancer

Copper ion is significantly involved in cancer biology, impacting various processes such as tumor growth, metastasis, and angiogenesis (Waldron et al., 2017; Gupta et al., 2020). While copper is an essential trace element necessary for normal cellular functions, its dysregulation is frequently observed in cancerous tissues, making it a potential therapeutic target (Chasapis et al., 2020; Schaefer et al., 2019). Studies indicate tumors often contain higher copper levels than surrounding healthy tissues (Petris et al., 2017). This elevated copper concentration is associated with increased angiogenesis, forming new blood vessels that supply tumor nutrients (Bontempo et al., 2016; Clegg et al., 2021). Copper promotes angiogenesis by facilitating the proliferation and migration of endothelial cells, which are essential for blood vessel formation (Waldron et al., 2017; Gupta et al., 2020). Research has shown that copper-dependent enzymes, such as lysyl oxidase, play a vital role in the maturation of the extracellular matrix, a crucial component in angiogenesis (Fischer et al., 2018).

Furthermore, copper ions are essential for the proliferation and survival of cancer cells. They participate in various signaling pathways, including activating hypoxia-inducible factors (HIFs), which regulate genes related to cell survival in low-oxygen environments. HIFs can enhance tumor growth and treatment resistance by increasing the expression of vascular endothelial growth factor (VEGF), a key angiogenic factor (Kopelovich et al., 2017).

Copper's relationship with cancer also involves its role in oxidative stress. Although copper is required for the activity of antioxidant enzymes, excessive copper can lead to oxidative damage and DNA mutations, contributing to cancer development. Increased oxidative stress may result in genomic instability and the activation of oncogenes, further promoting tumor formation (Harris et al., 2012). Elevated copper levels in the serum of breast cancer patients suggest that copper could serve as a biomarker for the disease (Ofoegbu et al., 2020).

Copper Ion in Metabolic Disorders

Copper ions are essential trace elements that play critical roles in various metabolic processes within the human body (Holzer et al., 2018). Their involvement in enzymatic reactions is crucial for maintaining cellular function (Waldron et al., 2017), and imbalances in copper levels can lead to several metabolic disorders (Schaefer et al., 2019). Copper is a cofactor for several enzymes, including cytochrome c oxidase, and is vital for cellular respiration and energy production. A copper deficiency can impair the function of these enzymes, resulting in mitochondrial dysfunction and reduced energy production (Linder, 2010). This impairment is often associated with metabolic disorders such as obesity and diabetes, where energy metabolism is disrupted.

Additionally, copper influences lipid metabolism, impacting the oxidation of fatty acids and cholesterol levels. It synthesizes high-density lipoprotein (HDL), commonly known as "good cholesterol," essential for transporting cholesterol away from the arteries and reducing cardiovascular disease risk. Altered copper levels have been shown to affect lipid profiles and contribute to dyslipidemia, characterized by abnormal lipid levels in the blood (Harris et al., 2013).

Copper also plays a role in glucose metabolism. Studies indicate that copper deficiency can impair insulin signaling and glucose homeostasis, increasing the risk of insulin resistance and type 2 diabetes (Wang et al., 2016). Conversely, excessive copper levels can disrupt glucose metabolism and lead to metabolic abnormalities.

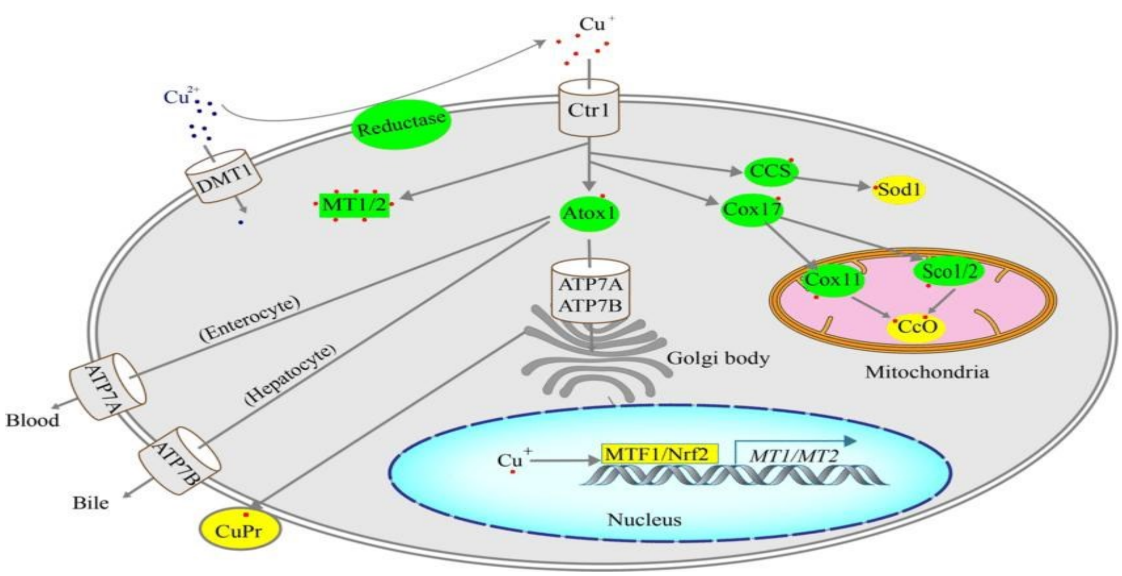

Figure 1.2 Schematic Diagram of Copper Ion in Metabolism Both in Cellular and Molecular Level

Copper Ion in Infectious Diseases

Copper ions are crucial in the immune response to infectious diseases due to their antimicrobial properties and role in various physiological functions (Gupta et al., 2020). They are essential for the immune system, influencing the activity of immune cells and contributing to the body's defense against pathogens (Holzer et al., 2018; Petris et al., 2017). Copper demonstrates direct antimicrobial effects against various bacteria, viruses, and fungi (Grass et al., 2011). Research has shown that copper ions can disrupt microbial membranes, leading to cell lysis and death (Rudolf et al., 2018). For instance, studies in various indicate that copper effectively inhibits the growth of Escherichia coli, Staphylococcus aureus, and Candida albicans by inducing oxidative stress and damaging cellular components (Grass et al., 2011; Schaefer et al., 2019). This antimicrobial property is particularly significant in clinical environments, where copper surfaces can help reduce the transmission of healthcare-associated infections (Waldron et al., 2017).

Additionally, copper is vital for the function of various immune cells, including neutrophils and macrophages. These cells utilize copper to generate reactive oxygen species (ROS), essential for eliminating engulfed pathogens. During an immune response, copper levels can rise in tissues, enhancing immune cell activation and their ability to fight infections (Rae et al., 2009).

However, the relationship between copper and infectious diseases is complex, as copper deficiency and excess can have adverse effects. A copper deficiency can impair immune function, increasing vulnerability to infections. For example, individuals with Wilson's disease, a genetic disorder marked by excessive copper accumulation, may experience immune dysfunction and a higher incidence of infections (Kaler, 2011).

Research from Nigeria has also underscored copper's role in infectious diseases. A study by Ogunlaja et al. (2020) found significantly elevated copper levels in the serum of tuberculosis patients, suggesting a potential link between copper and immune responses in infectious diseases. Another Study by Adeyemi et al. (2018) showed that breast cancer patients had significantly higher levels of serum copper compared to healthy individuals, suggesting that copper levels could serve as a marker for cancer progression. The study also suggests that copper chelation therapy could be an affordable and effective option for managing cancer, especially in low-resource settings.

Copper chelation therapies, like tetrathiomolybdate (TTM), are being tested for their potential to slow down tumor growth by preventing angiogenesis. Nigerian researchers also explore cost-effective copper chelation treatments for cancer care in resource-constrained environments (Lawal et al., 2021).

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Toxic Copper Ion and Environmental Health

Copper is an essential trace element, but excessive levels can result in toxicity that poses significant risks to both human health and the environment. Toxic copper ions can stem from various human activities, including mining, industrial operations, and agricultural practices, leading to soil and water contamination (Bontempo et al., 2016; Clegg et al., 2021). Copper toxicity can negatively impact human health, leading to various health issues, including liver damage and neurological symptoms (Tapia et al., 2020; Gupta et al., 2020). Acute exposure to high copper levels may cause gastrointestinal distress, liver damage, and neurological symptoms (Schaefer et al., 2019; Rudolf et al., 2018). Long-term exposure is associated with conditions like hepatic dysfunction and neurological disorders, including Wilson's disease, characterized by excessive copper accumulation in the body (Kaler, 2011).

In aquatic ecosystems, increased copper levels can harm aquatic organisms, disrupting physiological functions and decreasing biodiversity. Fish and invertebrates are especially vulnerable to copper exposure, which can impair gill function, slow growth rates, and affect reproduction. Research has demonstrated that copper toxicity can disrupt these organisms' enzyme activities and metabolic processes, leading to population declines (Baker et al., 2017).

Copper contamination can also have detrimental effects on soil health and agricultural productivity. Elevated copper levels can inhibit microbial activity and alter soil structure, impacting nutrient cycling and crop yields. Studies have shown that excessive copper in soils can reduce plant growth and hinder development, threatening food security (Li et al., 2016).

Increased copper levels in agricultural soils indicate that improper farming practices may contribute to copper accumulation, posing crop risks and potentially affecting human health throughout the food chain (Massimo et al., 2020).

Therapeutic Applications of Copper Ions

Copper ions have garnered attention for their therapeutic applications in various fields, particularly medicine and agriculture. Their unique properties enable them to be utilized in treatment modalities for several health conditions and as agents to enhance agricultural productivity (Waldron et al., 2017; Gupta et al., 2020).

In medicine, copper ions exhibit antimicrobial properties, making them effective against various pathogens, including bacteria, viruses, and fungi. This characteristic has led to the development of copper-throughout-infused materials for medical devices, wound dressings, and surfaces in healthcare settings (Grass et al., 2011; Clegg et al., 2021). Studies have demonstrated that copper surfaces can significantly reduce the survival of healthcare-associated infections, thereby minimizing the risk of infection transmission (Huang et al., 2015). Copper's efficacy against antibiotic-resistant strains of bacteria further highlights its potential as an alternative treatment option in the face of rising antibiotic resistance (Hunt et al., 2019).

Copper ion also plays a role in cancer therapy. Research indicates that copper can influence the growth and proliferation of cancer cells. Elevated copper levels are often observed in tumors, and targeting copper metabolism has emerged as a strategy for cancer treatment. Some studies suggest that copper chelation therapy may enhance specific chemotherapeutic agents' effectiveness by disrupting the copper supply to cancer cells (Gomez et al., 2020). However, the dual role of copper in promoting and inhibiting cancer cell growth necessitates further investigation to optimize its therapeutic use.

In agriculture, copper compounds are used as fungicides and bactericides to protect crops from diseases. Copper-based products, such as copper sulfate and copper oxychloride, have effectively controlled various crops' fungal infections and bacterial blights. Applying these compounds can enhance crop yields and quality while minimizing the reliance on synthetic pesticides (González et al., 2016).

Additionally, copper nanoparticles are gaining interest for their potential applications in drug delivery and as antibacterial agents in agricultural practices. These nanoparticles can enhance the bioavailability of certain drugs and provide targeted delivery, improving therapeutic outcomes (Fang et al., 2017).

Conclusion

Copper ion plays a crucial role in numerous biological processes, including enzyme activation, electron transfer, and oxygen transport. However, disturbances in copper homeostasis due to genetic mutations or environmental factors can lead to serious health issues, such as Wilson's disease, Alzheimer's, cancer, and metabolic disorders. As a transition metal, copper is involved in redox reactions, alternating between Cu(I) and Cu (II) oxidation states, essential for mitochondrial respiration, cellular defense against oxidative stress, and other vital biochemical processes. The disruption of copper regulation impairs these functions, contributing to the development of diseases. Continued research is necessary better to understand copper's role in health and disease and to develop effective treatments.

Recommendations

Raising public awareness through education and screening for early detection is important to address copper-related diseases.

Investment in research will improve understanding and treatments while developing affordable therapies essential for accessibility.

Promoting dietary changes can help prevent toxicity, and enhancing healthcare infrastructure will ensure better access to diagnostics.

Lastly, collaboration among researchers, healthcare providers, and policymakers is crucial for translating findings into effective clinical practices.

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