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Review

Copper mediated neurological disorder: Visions into amyotrophic lateral sclerosis, Alzheimer and Menkes disease

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ABSTRACT

Copper (Cu) is a vital redox dynamic metal that is possibly poisonous in superfluous. Metals can traditionally or intricately cause propagation in reactive oxygen species (ROS) accretion in cells and this may effect in programmed cell death. Accumulation of Cu causes necrosis that looks to be facilitated by DNA damage, followed by activation of P53. Cu dyshomeostasis has also been concerned in neurodegenerative disorders such as Alzheimer, Amyotrophic lateral sclerosis (ALS) or Menkes disease and is directly related to neurodegenerative syndrome that usually produces senile dementia. These mortal syndromes are closely related with an immense damage of neurons and synaptic failure in the brain. This review focuses on copper mediated neurological disorders with insights into amyotrophic lateral sclerosis, Alzheimer and Menkes disease.

Contents

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Introduction

Copper, an essential trace element responsible for diverse biological functions in human body [1]. Copper is present throughout the brain, with most prominent concentration in basal ganglia, hippocampus, cerebellum, numerous synaptic membranes, cell bodies of cortical pyramidal neurons and cerebellar granular neurons [2]. Copper is important for the normal development of the brain and nervous system, playing a crucial role in the production and maintenance of myelin [43,124]. Beside this it is also involved in neurotransmitter synthesis, for these reasons it plays an important role in nerve impulse transmission and neuronal communication [19,64,124,125]. At cellular level copper is required for respiration, peptide amidation, neurotransmitter biosynthesis, pigment formation, and connective tissue strength [3–5,125]. Copper is also an essential component of several important enzymes; the most studied enzymes are superoxide dismutase (SOD), [9–13], cytochrome-C oxidase, catalase, dopamine hydroxylase, uricase, tryptophan dioxygenase, lecithinase and other monoamine and diamine oxidases. Copper containing enzymes perform several functions in the body including oxidation–reduction reactions, transport of oxygen and electrons and the protection of the cell from oxygen radicals [14]. Role of oxidative stress has been implicated in the progression of several neurodegenerative diseases like Alzheimer's, Parkinson's and amyotrophic lateral sclerosis. Copper is also important for the prevention or moderation of certain neurodegenerative disease, including Parkinson's, Wilson's, Menkes, Alzheimer's [15] and prion diseases [16–24]. Copper deficiency may induce abnormalities including anemia, skeletal defects, degeneration of the nervous system, reproductive failure, pronounced cardiovascular lesions, elevated blood cholesterol, impaired immunity and defects in the pigmentation and structure of hair. Evidences suggest that changes in copper concentrations results in several neurological diseases [3,6–8,76].

Copper metabolism

Copper is readily absorbed from the diet across the small intestine (~2 mg/day) and stored in the liver. The major excretory route of copper stored in liver is via the biliary pathway (~80%) [25]. Copper is bound to either serum albumin or histidine and trafficked through the bloodstream for delivery to tissues or storage in the liver. Copper is imported into the hepatocytes via plasma membrane localized high-affinity human copper transporter (hCtr1) [26]. HCtr1 also participates in the intracellular compartmentalization of this metal. Once inside the cell, copper is escorted (i) to metallothionein pool or (ii) to the mitochondria for cytochrome-C oxidase incorporation or (iii) for delivery to emerging Cu, Zn-SOD or (iv) to the Wilson disease P-type ATP-ase in the trans-Golgi network for subsequent incorporation to the ceruloplasmin [27]. Ceruloplasmin contains about 95% of the copper found in serum [37].

Oxidative stress and copper

Copper can induce oxidative stress by two mechanisms. Firstly, it can directly catalyze the formation of ROS via a Fenton-like reaction [28,29]. Secondly, exposure to elevated levels of copper significantly decreases glutathione levels [30]. Cupric and cuprous ions can act in oxidation and reduction reactions. Cupric ion (Cu (II)), in the presence of superoxide anion radical or biological reductants such as ascorbic acid or glutathione (GSH), can be reduced to cuprous ion (Cu (I)) which is capable of catalyzing the formation of reactive hydroxyl radicals through the decomposition of hydrogen peroxide via the Fenton reaction [31–33].

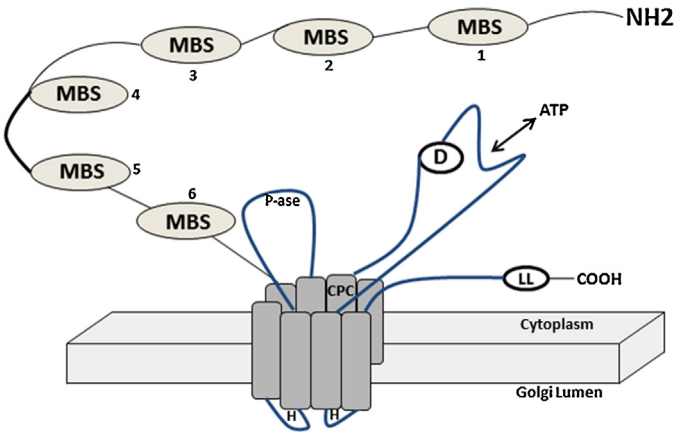

Fig. 1. Hypothetical model of ATP7A and ATP7B [43]. In this each molecule possesses six metal binding sites (Mbs) containing the GMTCxxC motif. Eight trans-membrane domains most likely form a channel for Cu (I) transport; one domain expresses a CPU motif which is crucial for Cu (I) transport.

$$Cu(II) + O_2^{\bullet -} \rightarrow Cu(I) + O_2 \quad (1)$$

$$Cu(I) + H_2O_2 \rightarrow Cu(II) + {}^{\bullet}OH + OH^- \quad \text{(Fentonreaction)} \quad (2)$$

The hydroxyl radical is extremely reactive and can further react with practically any biological molecules in the near vicinity, for example via hydrogen abstraction leaving behind a carbon centered radical, e.g. form a lipid radical from unsaturated fatty acids [37]. Copper is also capable of causing DNA strand breaks and oxidation of bases via ROS. Copper in both oxidative states (cupric or cuprous) was more active than iron in enhancing DNA breakage induced by the genotoxic benzene metabolite 1,2,4-benzenetriol. DNA damage occurred mainly by a site-specific Fenton reaction [34,74].

Glutathione (GSH) a powerful antioxidant present in the cell is a substrate for several enzymes that removes ROS. It has multiple functions in intracellular copper metabolism and detoxification. Glutathione can suppress copper toxicity by directly chelating the metal [35], maintaining it in a reduced state and making it unavailable for redox cycling [37]. Disruption of copper homeostasis results in elevated cellular copper levels which may contribute to shift redox balance more toward oxidizing environment by depleting glutathione levels [36,37,77]. The depletion of glutathione may enhance the cytotoxic effect of ROS and allow the metal to be more catalytically active, thus producing higher levels of ROS. The large increase in copper toxicity following GSH depletion clearly demonstrates that GSH is important cellular antioxidant acting against copper toxicity [38].

Copper in the brain

The mechanism of copper transport and homeostasis in the Central nervous system is still a matter of intense investigation. Copper correlates positively with brain development [39,40], entering the Central nervous system from the blood stream crossing the blood brain barrier (BBB). Copper-transporting ATPase were identified in studies on Menkes gene enabled us to understand the mechanism of copper transport [41,42]. Menkes disease is due to an inherited defect in copper absorption. Copper-transporting ATPase possesses six heavy metal-binding sites in the N terminal part of the molecule (Fig. 1) able to pump copper ions through physiological barriers (e.g. gastrointestinal mucosa and BBB).

After crossing the BBB, copper transport or distribution in glia and neurons is controlled by ATP7A protein and thus the metal