



Review Article

Dietary Copper for The Human Biological System and Brain: An Introductory Overview

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ABSTRACT

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The aim of this study was to conduct a review of dietary copper for the human biological system and brain. Copper is among the vital micronutrients that should be essentially consumed by humans through diet for proper functioning of the body (and brain in particular). Dietary copper is obtained from foods such as nuts, leafy green leaves, meat, grain cereals, etc. Most of the dietary copper is initially dependent on the environment (soil and water feeding the plant-based foods). Some people are born with inborn deformations (errors) of copper metabolism; parable, Menkes disease; in the brain, an array of neurodegenerative problems arises due to problem in dietary copper. Conspicuous of copper in the brain, especially in basal ganglia, cerebellum, synaptic membranes, hippocampus, cell bodies of pyramidal neurons are a clue of essentially of copper in brain functions as well. Neurodegenerative abnormalities of copper include, aceruloplasminemia, Alzheimer's disease, etc. The role of copper in enzymes such as cytochrome c oxidase, Cu, Zn- dependent superoxide dismutase, dopamine-beta hydroxylase, etc; and essentiality. Mostly, normal people may have normal copper, but deficiency occurs in patients such as those battling in Wilson's disease, celiac disease, etc. Therefore, people should be educated on how to wisely consume nutritious foods rich in micronutrients, including copper.



1 Introductory Copper Chemistry

Copper is a metal, an element of the third transition series, possessing an atomic weight and atomic number of 63.546 and 29 respectively. Two stable copper isotopes namely, ^{63}Cu and ^{65}Cu exist with natural abundance of 69.2 and 30.8% respectively. Copper exists in the following oxidative states:

- Copper (0), the metallic copper with a symbol of CuO .
- Copper (I), cuprous ion, the Cu^{2+} is unstable under neutral pH, that is Cu oxidize by air to give Cu^{2+}
- Copper (II), cupric ion, the Cu^{2+} that make $\text{Cu}(\text{OH})_2$ in water under alkaline pH (Stern et al., 2007)
- Copper (IV), a rare trivalent form

It is important to state that, the copper is significantly converted from Cu(I) to Cu(II) owing to its essentiality in disparate biological systems [1]. The aim of this study was to conduct a review of dietary copper for the human biological system and brain.

2 An Insight into The Metabolism of Copper by The Human Biological System

Human body obtain its copper through the diet sources such as nuts, chocolate, seafood, mushroom, leafy vegetables, leafy greens, legumes, and grain cereals among others [2, 3]. Copper is usually absorbed by the proximal portion of the small intestine and in turns the copper binds to amino acids (such as Asp, Gly, His, Cyst, Me, and Thr); and ligands. Probiotics such as inulin, fructo- oligosaccharides, and pectin are positive facilitators of copper absorption; while, Fe, Zn, Ca, molybdenum, vitamin C, and P may negatively affect copper absorption. Mostly, dietary copper is converted into reduced form

in a bid to allow the digestive system effectively absorb the copper. Cytochrome b reductase 1 (Cybrd1), cytochrome b reductase (558) Fe^{3+} , Cu^{2+} , transmembrane epithelial prostate are used in the reduction of the Cu^{2+} to Cu^+ for better absorption by the digestive system. Probably, Cu^+ ion is shuttled into the enterocytes using copper transporter 1 (CTR 1) (apical transporter dealing with the copper absorption from the lumen of the gastrointestinal tract, from the bloodstream into the enterocyte, and transport copper in- between cells). Other form of copper, that is the divalent ion is transported probably through the divalent metal transporter 1(DMT1) [4].

Copper enters the blood system (from the enterocytes) through the action of adenosine triphosphatase 7A (ATP7A), and it gets into cells through the CTR1 protein or relations. Inside the cells, copper (Cu^+) is subjected to sequestration by the tripeptide glutathione (GSH) and subsequently preserved in metallothioneins (Mats) (they exert high copper affinity due to possession of thiols). However, copper can be alternatively transported using the specific chaperones to reach specific targets (such as mitochondria, endoplasmic reticulum, nucleus, enzymes etc) [5]. The major responsibility of copper metabolism is shouldered by the liver and it houses most of the element as well. When there is excess copper, ATP7B (a similar component of ATP7A) present in liver cells move into the vesicles near the apical membrane to convey excess element into the bile. In circulation, copper usually exists in a bounded form to ceruloplasmin, proteins, amino acids, and peptides. Other remains of copper are exchangeable between albumin, alpha-macroglobulin, tissues, peptides, amino acids, organs (heart, kidney, brain etc). Bile and urine are used to remove excess copper from the body [5,6]. Copper is utilized by many enzymes as depicted in Table 1.

Enzyme	Function	Physiological Roles
Superoxide dismutase 1 (SOD1) and 3 (SOD3) *	Converts superoxide to hydrogen peroxide	Anti-oxidative defense
Dopamine-beta-hydroxylase	Catecholamine production	Regulation of autonomic nervous system
Monoamine oxidase	Pigment and neurotransmitter metabolism	Oxidation of monoamines
Cytochrome C oxidase COX (COX, complex IV of the respiratory chain)	Converts molecular oxygen to water	Energy metabolism
Tyrosinase	Production of melanin; conversion of tyrosine to L-DOPA	Protection of skin
Catalase	Conversion of hydrogen peroxide to water and oxygen	Prevents oxidative-induced damage in the heart
Glutathione peroxidase	Converts hydroperoxide and hydrogen peroxide	Antioxidative defense
Hephaestin (homolog of ceruloplasmin)	Ferroxidase activity	Control of iron efflux
Cartilage matrix glycoprotein (homolog of ceruloplasmin)	Involved in intestinal iron absorption	Synthesis of the extracellular matrix
Lysyl oxidase	Ferroxidase activity Oxidase activity	Stabilization of connective tissues
	Cross-linking of elastin and oxygen	

* Ceruloplasmin is a member of the multi-copper oxidase family of enzymes; * SOD1 and SOD3 contain catalytic copper and structural zinc ions in the active sites. SOD2 contains manganese as a metal cofactor.

Figure 1 Table 1: Some copper-requiring enzymes; Source: Manto, 2014:

3 Dietary Food Sources for Copper Intake

The presence of copper in food materials is related to the prevailing environment conditions such as soil copper levels, manure, industrial release of copper into the environment, agricultural use of copper compounds etc. The copper present in drinking water also varies according to environment (such as plumbing system, corrosion) [7]. However, despite the challenges, nuts, offals, cereals, milk, dairy products, fruits are sources of copper for consumption. Bost et al., (2016) [8] reported some specific sources of copper for human intake or consumption (see Table 2).

Table 2: Some dietary sources of copper

Food type	Concentration of copper in food type
Meat	
Liver, beef	2.1-43
Kidney, beef	0.1-1.8
Muscle, beef	0.1-9.1
Muscle, pork	
Cereals	
Maize	0.6-16.6
Wheat	2.9
Bread	3.4
Pasta	0.08-0.52
Vegetables	
Potato	0.48-16.0
Carrot	0.37-0.62

Peas	0.68-0.37
Lettuce	0.1-2.9
Tomato	0.1-3.4
Cabbage	0.1-7.7
Fruits	
Apples	0.1-2.3
Bananas	0.7-3.0
Oranges	0.8-0.9
Milk products	
Milk	0.1-0.88
Cheese	0.03
Processed cheese	0.025

Source: Bost et al., (2016).

4 Inborn Error in Copper Metabolism

Through studies over the years show that there are inborn-errors of copper metabolism in humans and relations. Some of these problems are related as follows:

Menkes Disease

In this disease patients can absorb copper into the intestine, but cannot shuttle into the bloodstream. Menkes Disease inborn error was initially discovered as an X-linked syndrome occurring approximately 1/200,000 births. It occurs mostly in boys and rarely in girls. It shows a significant systemic copper reduction or deficiency that may lead to death in young people and is coupled with severe neurological abnormality (due to reduced cytochrome c oxidase work) because many copper enzymes needed for brain development are absent. Hypopigmented hair (because of tyrosinase deficiency, leading to shortage of melanin), brittle hair, kinky (due to deficiency of enzyme

responsible for crosslinking keratin) [9]. It is also known with reduced lysyl oxidase efficiency and in turn causing abnormal collagens and elastin polymerization; and abnormalities of connective tissue (such as aortic aneurisms, fragile bones, loose skin). Early diagnosis and subsequent early intervention with specific copper compounds is believed to reduce the manifestation of neurological disorders and life expectancy can be extended. However, despite the early diagnosis affected patients could die before reaching 10 years old, some reach 20 years old, and some survived [1,7,10].

5 Copper Participates in Many Neurodegenerative Disorders in Humans

Copper is an essential metal required for body functioning. It is present all over the brain and mostly concentrated in the basal ganglia, cerebellum, synaptic membranes, hippocampus, cell bodies of pyramidal neurons, and cerebellar granular neurons. Many enzymes in the central nervous system relied on copper for their activities; for example, superoxide dismutase, hephaestin, cytochrome C oxidase, dopamine beta- hydroxylase, ceruloplasmin [7]. Some of the neurodegenerative disorders associated with copper are as enumerated below:

Aceruloplasminemia

Usually, ceruloplasmin carries 95% of the plasma copper and it behaves as ferroxidase. Aceruloplasminemia is an inborn autosomal recessive disorder associated with failure to incorporate copper into the apoceruloplasmin that is rapidly degraded and in turn spurring clinical situations such as dystonia, dementia, abnormal gait, and dysarthria [9,11].

Alzheimer disease

Alzheimer disease is characterized with a progressive cognitive impairment. Therewith, many patients with this disease show excess copper in cerebrospinal fluid and normal plasma copper levels. Most of the effects here are believed to be due to oxidative stress [1,9,12].

Huntington Disease

Huntington Disease is due to a tripartite repeat expansion of huntingtin and in turn oxidative stress, striated degeneration, and energy insufficiency. This disease is characterized with excess copper bound less to the

huntingtin and thereby instigating oxidative stress and neurodegenerative abnormalities [13].

Amyotrophic lateral sclerosis

This disorder occurs when there are gain-of-function mutations in the cystolic copper enzyme (the Cu/Zn superoxide dismutase). Selective neuronal respiratory problems; in turns death occurs. In this vein, free-radical accumulation was intensified due to copper excess levels [14].

Parkinson Disease

It is a popular neurodegenerative movement disease due to impaired functions (such as rigidity, postural instability, tremors). The pathology of the disease consists of dopaminergic neuron death, accumulated Lewy bodies (associated with alpha-synuclein mutation). Oxidative stress is a factor in this disease disorder as well [7].

Prion Diseases

They are group of diseases affecting grey matter in the central nervous system and in turns producing neuronal loss, spongiform degeneration, and gliosis. Prion Diseases occur due to improper folding of prion proteins and their accumulation in the central nervous system. In this vein, copper lead to accumulation of prion proteins thereby enhancing protease resistance, and infectivity [6].

Occipital horn syndrome

This is a disorder that is alternative form of Menkes Disease, but in a class of connective tissue (such as cutis laxa, bonus protuberances of occiput hyper-mobile joints). There is presence of decreased lysyl oxidase activity and in turns resulting in collagen and elastin cross-linkages [6].

Reduced released of norepinephrine leads to impaired innervation of postganglionic sympathetic and parasympathetic systems. Overall, the effects in occipital Horn syndrome are due to low serum copper, low ceruloplasmin, abnormal plasma, abnormal cerebrospinal fluid plasma, and abnormal cerebrospinal fluid catecholamine level [6,15].

6 Copper relates with synaptic function

Copper's role in central nervous system is inevitable. In disparate studies argued by Opazo et al., (2014) [16] it was revealed that copper exert effects on brain synapses, because it leads to inhibition of longterm potential (LTP),

and receptor biochemistry. Thus, it can be echoed that, synaptic configuration adequately responds to changes in copper level [16].

7. Copper Level in the Brain

Every human needs copper for proper functioning of the brain and other parts. However, the brain needs copper more than any other body part except the liver. About 2.9 to 10.7ug Cu/g wet weight is present in human brain; therewith, the entire major compartments of the brain contain copper, but hippocampus contains higher level [17]. Therefore, copper level in different brain compartments may be linked to metabolic demand specific to every region and compartment; usually, concentrations are altered according to growth stages of the human body. The younger ones require more copper supply, of which failure to obtain right amount could lead to devastating consequences [15,18,19].

8. Copper Enzymes Are Essential to Central Nervous System

It is notable that, central nervous system utilizes copper for metabolisms such as in the case of respiration, oxidative defense, production of neuroendocrine peptides, and hormones synthesis as well [19]. Copper dependent enzymes, such as cytochrome C oxidase (CCO), and Cu, Zn- dependent superoxidodismutase (SOD1) protect the brain against oxidative stress in the cytosolic medium [17]. Primarily, peptidyl-alpha-amidating monooxygenase (PAM), and dopamine-beta-hydroxylase (DBH) essentially ensure amidation of neuropeptides and making of norepinephrine. The functioning of hormones and neurotransmitters (for example, gastrin, oxytocin, corticotropin-releasing factor) require amidation [17]. Other

copper-dependent enzymes present in the brain include, lysyl oxidase (perform an oxidation of side chain of lysine in collagen and elastin formation), multi copper oxidase ceruloplasmin, etc [17,20,21].

9. Copper Imbalance Lead to Severe Consequence Symptoms

of copper toxicity include, vomiting, anemia, abdominal pain, tachycardia. Disparate situations of copper imbalance especially during young days lead to long lasting effects in humans. Insufficiency of copper could lead to effects such as anemia, motor neuron disease, neurological manifestations, myeloneuropathy, loss of myelin, delayed myelination, reduced angiogenesis [5,12,23]. However, copper overload is also a monumental consequence, for example, Menkes disease, and Wilson disease, are typically demonstrations of copper overload consequence [7,23].

10. People at Risk of Copper Deficiency

Copper deficiency is a rare phenomenon among humans. Many patients due to several conditions could be affected by copper deficiency. Parable, patients with situation of excess zinc intake, penicillamine intake, occipital horn disease, Wilson's disease, celiac disease, etc could experience copper deficiency [19,22]. Those groups of people and others could be help through supplementation interventions. Other people at risk of copper deficiency include, people consuming single diet, people consuming antacids regularly, people consuming poor diet, people from poor background [4,24].

Lab Parameter	Initial Clinic Visit Jan. 2018	3 Weeks Later Post Copper Repletion
White blood cells (k/uL) (reference: 4.00 – 11.00 k/uL)	1.89 (↓)	6.09
Hemoglobin (g/dL) (reference: 14.0 – 18.0 g/dL)	11.9 (↓)	12.2 (↓)
Platelets (k/uL) (reference: 150 – 450 k/uL)	95 (↓)	161
% neutrophils (Calc. %) (reference: 47 – 82%)	44.5% (↓)	69.3%
Abs. Neutrophil count (/uL) (reference: 1800 – 8000/uL)	890 (↓)	4220
Copper (mcg/mL) (reference: 0.75 – 1.45 mcg/mL)	<0.10 (↓)	0.91
Ceruloplasmin (mg/dL) (reference: 25.0 – 63.0 mg/dL)	<6.0 (↓)	23.7 (↓)

Table 2. Patients at Risk For Copper Deficiency^{4,8-11}

- ◆ Gastrectomy/gastric surgery bypassing duodenum & between 100-200cm of jejunum (primary site for copper absorption)
 - Roux-en-y gastric bypass in particular with patients supplemented with zinc and no copper
 - Jejunio-ileal bypass
- ◆ Celiac disease
- ◆ Excess zinc ingestion
 - Ingestion of pennies secondary to Pica
 - Denture cream
 - Zinc supplements
 - Chronic use of zinc containing cold remedies (such as Cold-EEZE, Zicam, or other zinc lozenges)
- ◆ Parenteral nutrition without or insufficient copper added
- ◆ Enteral feeding
 - Inadequate copper content of formula, or volume provided does not contain enough copper for that individual
 - Jejunal access
- ◆ Prolonged continuous renal replacement therapy (CRRT) (> 2 weeks)
- ◆ Nephrotic syndrome – excess loss
 - Increased permeability of glomerulus to ceruloplasmin
- ◆ Penicillamine
 - Facilitates renal copper excretion through chelation
- ◆ Alkaline therapy for renal tubular acidosis
- ◆ Menke’s kinky hair disease
 - X-linked recessive multisystemic lethal disorder of copper metabolism
- ◆ Occipital horn disease
 - Occipital horn syndrome, formerly considered a variant of Ehlers-Danlos syndrome, an X-linked recessive connective tissue disorder; considered a milder variant of Menkes disease
- ◆ Wilson’s disease
 - Serum copper is low, which may seem paradoxical given that Wilson’s disease is a disease of copper excess, however it is sequestered in the liver; 95% of plasma copper is carried by ceruloplasmin which is often low in Wilson’s disease

Figure 2: Patients at risk of copper insufficiency (deficiency), Source: Parrish & O’Dannell, (2020)

General Suggestions

- RDA = adult men and women is 900µg/day
- ◆ Do not take with iron or zinc supplements – if patient needs both, take them at different times of the day
- Recheck serum copper in 4 weeks
- Do not check too soon after beginning supplementation.
- Net amount absorbed increases as the amount in diet increases, but absorption is more efficient when intake is low.

Route	Copper Supplement Dose	Comments
Oral / Enteral	Copper gluconate	◆ 2-8 mg daily or every other day
	Copper sulfate	◆ May not be well absorbed in alkaline medium
	Copper citrate	◆ Most common type of dietary copper on the market; concerns about bioavailability
	Chelated copper (glycinate or bisglycinate)	◆ A complex consisting of elemental copper and another molecule (typically an amino acid); claims to be more bioavailable, passing easily through intestinal tract and directly into bloodstream (no scientific proof available).
	Copper oxide	◆ Low bioavailability
	Cocoa powder	◆ 10 g pure cocoa powder (4 teaspoons)
IV		◆ Some reports of tachycardia
	Copper gluconate	◆ 1.5-4 mg over 2 hours x 5-6 days ◆ In those refractory to IV repletion, consider retention of IV copper may improve if infused over a longer period of time (8-12 hours) like magnesium.
	Copper chloride	◆ Used as an additive to TPN

Figure 3: Copper supplementation to overhaul insufficiency Source: Parrish & O’Dannell, (2020)

11. Metabolism of Copper in the Brain

Due to the role of copper in development, functions, maturation; copper could enter the brain with the aid of blood brain bilayer (BBB). However, regulation of copper intake by the brain could be done by cerebrospinal

barrier (CSF). Upon uptake by the brain, copper is transported specifically by copper transporter 1 (CTR1), and cling to the copper- metal chaprone (CCS), and then shuttles to SOD1; thereafter, copper is transported to copper transporting ATPases. The ATPases have to be responsible for shuttling the copper to the copper-requiring enzymes. Additionally, glutathione could facilitate the regulation of cellular copper pool [19,25].



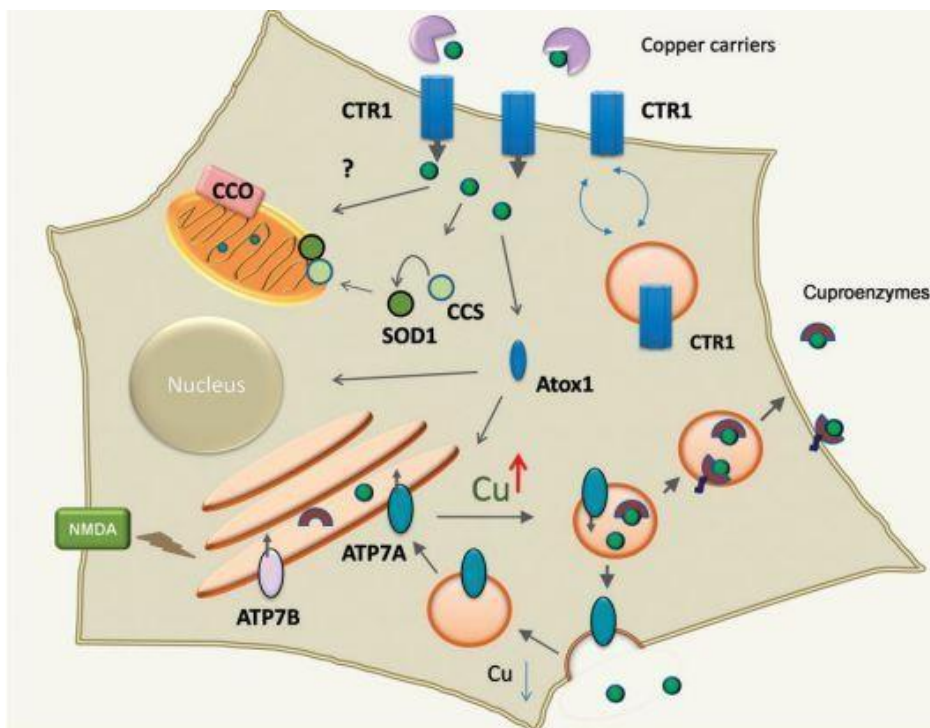


Figure 4: General distribution of copper in CNS cell; Source: Lutsenko et al., (2010).

12 Conclusion

Micronutrients are essential for diverse functions of the human body. Parable, copper is a common essential micronutrient essential in human body functioning and has to be imported through food. Various body functioning and has to be important through foods. Various body enzymes such as tyrosinase, catalase, glutathione peroxidase, lysyl oxidase, hephaestin, cytochrome c oxidase, etc need copper to exert their various functions. The brain significantly utilize copper and any imbalance in copper metabolism could manifest in form of diseases or abnormalities. Albeit, copper deficiency in humans is rare, but many human patients could be affected. Therefore, it is important to say the least, that copper should be properly consumed through foods to help body parts function well especially in youngsters.

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