Copper in the Human Body

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Copper, an essential trace element found in the brain, liver, and kidneys, enables the body to form red blood cells, maintain bone health, and can help prevent cardiovascular disease and osteoporosis. Copper is also a key element in maintaining lung function as it plays a vital role in metabolic processes such as cellular respiration.

copper

1. Copper

Copper, an essential trace element found in the brain, liver, and kidneys, enables the body to form red blood cells, maintain bone health, and can help prevent cardiovascular disease and osteoporosis. Copper is also a key element in maintaining lung function as it plays a vital role in metabolic processes such as cellular respiration [2]. Copper stored in the human body can be used for protein and energy production [3][4]. For adults, healthy copper levels range between 50 and 80 mg; levels exceeding this range are considered toxic and can lead to a buildup of copper in the kidneys, brain, and eyes. This causes a burden on the body as it may result in possible liver cell death, permanent nerve damage, oxidative stress, and reduced cell proliferation [3][5]. A lethal dose of copper ranges from 10 to 20 g [5]. Common signs of copper toxicity include, but are not limited to, headaches, bloody vomit, diarrhea, and black stools.

In the bloodstream, copper exists in two forms: 85 to 90 percent of copper found in the blood is bound to ceruloplasmin, a protein that plays a role in iron metabolism; the remaining 10 to 15 percent is free-floating copper, sometimes loosely bonded to other molecules [5][6]. Copper toxicity may occur as a result of various exposures. Common means of excess copper exposure occur from consumption of acidic foods cooked in uncoated copper cookware, exposure to excess copper in drinking water, breathing air or dust containing copper, as well as other environmental sources [5][7]. Other instances include copper salt topical creams for burn treatment, as well as in farming as a pesticide, and the leather industry [5].

Several genetic disorders are associated with copper related diseases. Examples of such illnesses include Wilson’s disease and Menkes disease. Wilson’s disease, a genetic disorder where the body is unable to filter out excess copper and therefore builds up in body tissue, occurs due to mutations in the ATP7B gene [6]. ATP7B codes for the protein ATPase 2, a copper-transporter found in the liver and brain [6][8]. This mutation can result in hepatic toxicity as well as adverse effects on the central nervous system, disrupting homeostatic bodily functions [6]. Similarly, Menkes disease, an X-linked recessive disorder, is a result of mutation in the ATP7A gene; the purpose of

ATP7A is to code for copper regulation and copper absorption from food [8]. Symptoms of Menke's induced copper deficiency include hair loss, slow growth and development, and neurological effects [8].

2. Role of Copper in the Human Body

Copper is an element essential to the homeostasis of the human body due to its role in energy production, iron metabolism, neuropeptide activation, and connective tissue and neurotransmitter synthesis [9]. Copper's most crucial property however is its role in cuproenzyme ceruloplasmin [10]. Ceruloplasmin is the major copper-carrying protein in the blood, accounting for over 95% of copper transport in human plasma [9][10]. Studies have also found that copper plays a crucial role in the formation of red blood cells, immune system function, brain development, gene expression, and other physiologic processes [9]. Through the use of ceruloplasmin transport, copper is able to reach the brain, which uses a significant portion of copper found in the body for brain development and regulation of the nervous system [6][9][10]. Copper is also significantly used in the liver to convert iron into its ferric form as well as absorb iron into the gut [6].

3. Common Forms of Copper Intake

Copper toxicity is an associated result of exposure to copper contaminated sources. Common exposure sites include water supplies, copper pipes, uncoated copper cookware, birth control, dietary supplements, food, and fungicides. Water supplies are often contaminated by farm operations and other industrial waste practices that become runoff and enter reservoirs and public wells [11]. This waster is then transported to nearby populations for consumption and other daily activities. Such an instance was accounted for in a 2016 journal highlighting the widespread water contamination of heavy metals, specifically copper and lead, in New South Wales, Australia [11]. This study analyzed tap water from 212 different homes in the region; of these samples, almost 100 percent tested positive for copper, with 5 percent testing positive for excess copper [11]. For the houses testing within the normal copper range, it was also found that drinking water contributed to 6 to 13 percent of the average daily intake of copper [11]. A high copper positive percentage was expected since many of these homes utilize copper pipes and fittings for water supply [11]. Subsequently, copper pipes are a great cause of concern regarding copper contamination as acidic water may cause erosion of the pipe or fitting, releasing copper particles directly into the water [11]. Therefore, this study concluded there is a great concern for copper levels due to their frequent occurrence at high concentrations, as this water is then used for drinking, washing of cookware, as well as for bathing, and personal hygiene, creating various opportunities for direct ingestion of copper contaminated water, increasing the prevalence of copper toxicity in the region [11]. Other sources of copper contamination include improperly coated copper cookware, such as pots and pans. If not coated with another non-reactive metal, copper from the cookware can enter food and therefore the human body. As copper levels in the body increase, excess copper begins to pool in tissues, leading to copper toxicity. Similar to copper pipes, unprotected copper cookware can corrode in the presence of acidic foods, resulting in another means of entry into the human body [5]. Copper toxicity can also be caused through the use of birth control, as it can raise copper levels, which also destroys Vitamin C, another essential nutrient for the human body's optimal function [12]. Dietary supplements and other

foods can also be a source of excess copper. The recommended daily dose of copper for those aged 19 and older is 900 mcg, with the upper limit at 10,000 mcg [6]. Overconsumption of copper supplements or foods high in copper content, such as legumes, mushrooms, chocolate, liver, and nuts and seeds, can result in copper toxicity when not consumed in moderation [6]. Copper sulfate, an inorganic copper and sulfur compound used as a fungicide and algaecide in swimming pools, creates a toxic environment for microorganisms that kill small plants and animals by shocking roots and causing copper toxicity, respectively [13]. Due to its multiple points of entry into the human body, copper contamination is a growing concern, especially considering the large quantities in which it is found in the activities of daily life.

4. Alzheimer's Disease and Copper Pathways

The adult human brain contains approximately 100 billion neurons, directly correlating with brain mass. As healthy aging occurs, neurogenesis, the process of regeneration by neural plasticity, slows down, and neuron proliferation rate decreases [14]. Dementias, such as Alzheimer's, can speed up neurodegenerative processes, causing memory loss, progressing to the point where the patient is no longer capable of independently performing activities of daily living. Referred to as cerebral atrophy, the loss of neurons decreases brain mass overall or in specific areas [15]. Alzheimer's disease begins by targeting the hippocampus and entorhinal cortex located in the temporal lobe [1][16]. The temporal lobe is responsible for the connection of the network responsible for memory, navigation, and the perception of time [16]. The targeting of this region decreases the number of transmitters in the temporal lobe, causing neuron death and therefore size reduction, which can be seen on MRI scans of the brain [16]. A 2020 study found that the temporal lobe of those with Alzheimer's disease decreases at a rate of 15.1 percent per year whereas the normal neurodegeneration rate is a significantly lower 1.5 percent [17]. The study concluded that cognitive decline and subsequent memory loss are a direct result of temporal lobe atrophy [17]. As the disease progresses, the cerebral cortex also becomes impaired [1][18]. The cerebral cortex is the outer layer of neural tissue located at the front of the head, covering the outer portion of the cerebrum [19]. The cerebrum controls language, reasoning, social behaviors, emotion, muscle movement, hearing, vision, and other sensory controls [1][19]. Alzheimer's disease can also be characterized by neural mass loss and astrocytosis in the cerebral cortex [1][18]. A 2018 study found that about 25 percent of individuals who die by the age of 75 presented with substantial cerebral lesions resembling those of Alzheimer's disease [18]. This study concluded that the identification of cellular brain structure is essential to understanding neurodegenerative disease progression [18]. The order of progression for Alzheimer's disease begins in the hippocampus and expands outward to the temporal lobes, frontal lobes and prefrontal cortex, parietal lobes, occipital lobes, cerebellum, and finally the brainstem [20]. Once the disease reaches the brain stem, autonomous functions of the body will cease, ultimately proving fatal [20].

Copper toxicity results in the pooling of copper in different tissues of the body [3][5][21]. Prominent areas of copper pooling include the liver, brain, and eyes [5]. A 2013 study of male Wistar rats conducted by Pal et al. found copper toxicity effects on the rat brain include swelling and increased number of astrocytes, star-shaped glial cells, and copper deposition in the choroid plexus, which is located in close contact with the cerebral cortex [22][23]. The study concluded that copper toxicity in male Wistar rats causes impaired spatial memory and neuromuscular

coordination, swelling of astrocytes, copper deposition in the choroid plexus, neuronal degeneration, and augmented levels of copper in the hippocampus [22]. This is a significant finding due to the implications of these symptoms; impaired spatial memory and neuromuscular coordination can result in difficulty walking and navigating, swelling of astrocytes can result in brain edema and fulminant hepatic failure, impairment of the choroid plexus can cause variations in the development of cerebrospinal fluid possibly leading to overproduction causing pressure in the brain, neuronal degeneration can lead to neuron death, and augmented levels on copper in the hippocampus can lead to various dementias [24][25][26][27]. Dementias may be a result of the various plaques copper can induce, the most prevalent of which are amyloid-beta plaques associated with Alzheimer's disease [28]. Another 2018 study, conducted by Kardos et al., found copper levels to be significantly higher in the cerebellum, choroid plexus, ventricle system, and substantia nigra, a region of the midbrain [29]. This study also found that free excess copper often pools in the soma of cerebellar granule and cortical pyramidal neurons, as well as the hippocampus and spinal cord [29]. One 2012 study analyzed possible reasons for high copper levels in the brain and theorized that a high-fat diet caused an increase in copper levels, which they theorized was also correlated to an increased risk of Alzheimer's disease [30]. The study found that the highest 20 percent of those with copper intake lost cognition at six times the rate of groups with lower copper consumption if they also had a high-fat diet [30]. The study hypothesized that the ingestion of free-floating copper from sources such as drinking water and copper supplements played a major factor in the onset of Alzheimer's as it caused high levels of copper pooling in the brain [30]. This study concluded that there is a strong correlation between copper levels and the prevalence of Alzheimer's disease [30]. It is believed this correlation exists due to the commonalities between affected areas by Alzheimer's disease and copper toxicity [29][30]. Such common areas include the hippocampus, cerebral cortex, cerebellum, and brainstem, which affect memory, information processing, motor skills, and regulation of autonomous functions, respectively [20][29][30]. This supports the theory that copper may play a role in the onset of Alzheimer's disease as these regions are also the pathway of the general progression of the disease [20].

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