27. Copper

Physiology

The two oxidation states of copper enable it to participate in electron-transferring (oxidase) enzyme activities such as cytochrome oxidase, Cu/Zn superoxide dismutase, thioloxidase, and amine oxidases/ monophenol monooxygenases, e.g. DOPA oxidase and lysyl oxidase. Thus it is essential for cellular energy metabolism, the production of connective tissue and synthesis of neuroactive peptides (catecholamines and enkephalins) [1,2,3].

The total body copper in adults is 50-120 mg of which approximately 15 %, 10 % and 40 % are located in liver, brain and muscle respectively. In plasma (copper content 10-25 μmol/L) 90-95 % of copper is bound to caeruloplasmin, the remainder is bound to albumin, transcuprein and free amino acids.

The precise function of caeruloplasmin is unknown. It may participate in the peripheral distribution of copper as may transcuprein and free amino acids. Additionally caeruloplasmin has numerous oxidase activities, substrates for which include biogenic amines, adrenaline, serotonin, ascorbate, and sulphydryl groups, and its oxidation of $Fe(II)$ to $Fe(III)$ and $Mn(II)$ to $Mn(III)$ may be essential for the binding of these metals to transferrin. It may also serve as a plasma free radical scavenger.

Intestinal uptake and transfer of copper occur predominantly in the small intestine, where, as with other trace metals, it is probably presented to the mucosa bound to low molecular weight ligands. Intestinal absorptive efficiencies of between 35 and 70% have been reported.

Systemic homoeostasis of copper is achieved by adjustment of biliary excretion; 0.5-1.5 mg of the element is lost by this route daily. Intestinal adaptation also contributes and with high copper intakes an intestinal block of copper absorption mediated by metallothionein may occur [4].

Deficiency and excess

The features of severe copper deficiency can be related to loss of specific cuproenzyme activities [5]. The typical syndrome of copper deficiency has occurred in

preterm infants, in normal term infants who have been inappropriately fed on unmodified cow milk, in children recovering from malnutrition and in adults and children receiving parenteral nutrition. Features of copper deficiency in infants and young children include neutropenia, leucopenia and skeletal abnormalities, and increased susceptibility to respiratory and other infections [6]. Anaemia may develop if deficiency is prolonged and severe.

The occurrence of dietary copper deficiency in adults is far less well documented. Some systematic studies of copper deprivation have excited interest that low intakes may contribute to cardiovascular diseases [7,8]. These defects include impaired cardiac function and dysrhythmias perhaps secondary to defective metabolism of catecholamines and enkephalins [3]; such defects and the contribution of "sub-optimal" copper intake to atherogenesis need further metabolic evaluation.

Copper toxicity arises from deliberate ingestion of copper salts, or accidentally from contamination of drinks. In acute toxicity the gastrointestinal tract is affected, variable degrees of intravascular haemolysis, heptocellular necrosis and renal tubular failure result and death may ensue [1,9].

With chronic exposure copper accumulates in the liver and toxicity is insidious. Eventually hepatic necrosis or cirrhosis with liver failure develops. Some infants and young children, at least, are vulnerable to high intakes arising from the use of copper containers and conduits [9].

Copper taken as copper sulphate induces nausea at intakes of 10 mg and intakes above this are increasingly emetic [1]. However when consumed with foods the element is better tolerated and it has been suggested that intakes of 10 to 35 mg/d could be tolerated. These suggestions, however, have not been verified and for the moment an upper limit of 10 mg/d is proposed.

Requirements

There are limited data on which human copper requirements can be based. A review of published balance studies suggests that balances can be achieved at intakes around 1.2 mg copper daily (CF Mills, personal communication). Copper-responsive clinical and biochemical defects have been seen in adults on experimental intakes of 0.7-1.0 mg/d for four weeks or more. However it is possible that some of these abnormalities may have arisen from the nature of the experimental diets [7], and another study using more customary, although still experimental, diets found no deterioration of current indices of copper supply in men on intakes of 0.79 mg/d for 42 days [11]. This suggests that 0.8 mg Cu/d is an adequate intake although actual

requirements may be lower. For example, for adults on parenteral nutrition 0.3 mg/d is adequate [12]; at an absorbability of 50 % this could correspond to a dietary intake of 0.6 mg/d. Such evidence suggests that an Average Requirement of 0.8 mg/d could be set with a LTI of 0.6 mg/d and, with an allowance for possible storage requirements, a PRI of 1.1 mg/d. Dietary intakes are generally 1.0-1.5 mg daily.

Children

Requirements for infants 6-11 months have been calculated on the basis of a tissue content of 1.38 μg/g [13], and an adjustment to allow for a possible loss of endogenous copper [14]. An absorption of 50% is assumed, to give a PRI of 36 μg/kg/d. PRIs were calculated from the interpolated values of 30 μg/kg/d at 1-6 years, 24 μg/kg/d at 7-10 years, and 18 μg/kg/d at 15-17 years.

Pregnancy

The estimated requirements for the products of conception are 0.033, 0.063 and 0.148 mg/d for the first, second and third trimesters respectively [15]. It is considered that these can probably be met by metabolic adjustment by the mother, so no increment is proposed for pregnancy.

Lactation

If 750 ml milk is produced with a copper content of 0.22 mg/L [16], and absorption is 50%, an increase of 0.33 mg/d would be required in the diet to support lactation.

Summary

Adults	mg/d
Average Requirement	0.8
Population Reference Intake	1.1
Lowest Threshold Intake	0.6

Population Reference Intakes of other groups

Age Group		PRI (mg/d)
	6-11m	0.3
	1-3 y	0.4
	4-6 y	0.6
	7-10 y	0.7
Males	11-14 y	0.8
	15-17 y	1.0
Females	11-14 y	0.8
	15-17 y	1.0
	Pregnancy	1.1
	Lactation	1.4

References

1. Mason KE. (1979). A conspectus of research on copper metabolism and requirements of man. *J Nutr*, **109**: 1979-2066.

2. Prohaska JR. (1988). Biochemical functions of copper in animals. In: Prasad A, ed. *Essential and Toxic Trace Elements in Human Health and Disease*. New York: Alan R Liss, 105-124.

3. Bhathena SJ, Recant L, Voyles NR, Timmers KI, Reiser S, Smith JC, Powell AS. (1986). Decreased plasma enkephalins in copper deficiency in man. *Am J Clin Nutr*, **43**: 42-46.

4. Cousins RJ. (1985). Absorption, transport and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. *Physiol Rev*, **65**: 238-309.

5. Danks DM. (1988). Copper deficiency in humans. *Ann Rev Nutr*, **8**: 235-257.

6. Castillo-Durán C, Fisberg M, Valenzuela A, Egaña JI, Uauy R. (1983). Controlled trial of copper supplementation during the recovery from marasmus. *Am J Clin Nutr*, **37**: 898- 903.

7. Reiser S, Smith JC, Mertz W, Holbrook JT, Scholfield DJ, Powell AS *et al.* (1985). Indices of copper status in humans consuming a typical American diet containing either fructose or starch. *Am J Clin Nutr*, **42**: 242-251.

8. Klevay LM, Inman L, Johnson LK, Lawler M, Mahalko JR, Milne DB *et al.* (1984). Increased cholesterol in plasma in a young man during experimental copper depletion. *Metabolism*, **33**: 1112-1118.

9. Spitalny KC, Brondum J, Vogt RL, Sargent HE, Kappel S. (1984). Drinking-water-induced copper intoxication in a Vermont family. *Pediatrics*, **74**: 1103-1106.

10. Müller-Höcker J, Meyer U, Wiebecke B, Hübner G, Eifer R, Kellner M, Schramel P. (1988). Copper storage disease of the liver and chronic dietary copper intoxication in two further German infants mimicking Indian Childhood Cirrhosis. *Pathol Res Pract*, **183**: 39-45.

11. Turnlund JR, Keyes WR, Anderson HL, Acord LL. (1989). Copper absorption and retention in young men at three levels of dietary copper by use of the stable isotope ⁶⁵Cu. *Am J Clin Nutr*, **49:** 870-878.

12. Shike M, Roulet M, Kurian, Whitewell J, Stewart S, Jeejeebhoy KN. (1981). Copper metabolism and requirements in total parenteral nutrition. *Gastroenterol*, **81:** 290-97.

13. Widdowson EM, Dickerson JWT. (1964). Chemical composition of the body. In: Comar C, Bronner F, eds. *Mineral Metabolism: An Advanced Treatise*. Vol.2, New York: Academic Press, 1-247.

14. Zlotkin SH, Buchanan BE. (1983). Meeting zinc and copper intake requirements in the parenterally-fed preterm and full-term infant. *J Pediatr*, **103:** 441-446.

15. Shaw JCL. (1980). Trace elements in the fetus and young infant. II Copper, manganese, selenium and chromium. *Am J Dis Child*, **134:** 74-81.

16. Casey CE, Neville MC, Hambridge KM. (1989). Studies in human lactation: secretion of zinc, copper and manganese in human milk. *Am J Clin Nutr*, **49:** 773-785.