Copper in mammals: mechanisms of homeostasis and pathophysiology

Michael A. Cater and Julian F.B. Mercer

Abstract

The ability of mammals to tightly regulate systemic copper levels is vital for health as demonstrated by the severity of the genetic copper deficiency and copper toxicity disorders, Menkes disease and Wilson disease, respectively. Analysis of these genetic disorders has led to a substantial increase in the understanding of the role of copper in health and disease. The isolation of the genes involved in these diseases and use of yeast mutants with altered copper and iron homeostasis has revealed a range of molecular mechanisms governing copper homeostasis. These mechanisms include regulation of cellular copper uptake and efflux and involve the use of chaperones for safe intracellular copper distribution. Here we provide an overview of the physiological role of copper and the molecular mechanisms regulating systemic and cellular copper levels in mammals. Furthermore, we discuss the pathophysiological mechanisms and consequences of copper deficiency/overload in relation to disease.

1 The biochemical properties of copper

Copper exists physiologically in two redox states, as cuprous Cu^{1+} (reduced) or cupric Cu^{2+} (oxidized) and can interchange between these forms by accepting or donating an electron. This allows the cation to participate in biochemical reactions as a reducing or oxidizing agent (Alberts et al. 1995). In mammals there are over 30 known proteins that bind copper (Solioz 1998), and many of these proteins are enzymes that utilize copper as a cofactor in single-electron-reactions. Several of the important copper dependent enzymes are shown in Table 1. Despite the oxidative capacity of copper being essential for various enzymatic reactions, this property also makes the cation potentially toxic. Ionic copper can catalyse the production of free radicals, in particular, the highly reactive hydroxyl radical through Fenton chemistry, which subsequently can damage lipids, proteins, DNA and other biomolecules (Yoshida et al. 1993). Therefore, it is imperative that the level of copper in the body is strictly regulated and that the delivery of copper to enzymes that require the cation occurs in a manner that avoids oxidative damage.

Topics in Current Genetics, Vol. 14
M.J. Tamás, E. Martinoia (Eds.): Molecular Biology of Metal Homeostasis and Detoxification
DOI 10.1007/4735_101 / Published online: 11 August 2005

Table 1. Mammalian copper-dependent proteins

Common name	Major localization	Enzymatic function	Consequence of deficiency/defect
Ceruloplasmin	Plasma	Converts ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) through ferroxidase activity	Defective iron transport and metabolism, anemia, haemosiderosis
Lysyl Oxidase	Extracellular fluid, cartilage, bone and blood	Connective tissue synthesis (cross-linking of collagen and elastin)	Connective and skeletal tissue defects resulting in arterial weakness, bladder diverticulae, loose skin and joints, osteoporosis, emphysema
Tyrosinase	Melanocytes of eye and skin	Pigment (melanin) synthesis	Depigmentation
Dopamine-β-hydroxylase	Catecholamine storage vesicles in neuron synapses	Neurotransmitter synthesis, conversion of dopamine to acetylcholine (noradrenaline)	Hypothalamic imbalance resulting in hypothermia, anorexia, respiratory failure, somnolence, dehydration, ataxia
Cu/Zn superoxide dismutase (SOD)	The cytoplasm and mitochondria	Free radical detoxification, dismutation of superoxide radicals	Oxidative stress to cellular component resulting in central nervous system degeneration and mitochondrial defects
Cytochrome c oxidase	Inner mitochondrial membrane	Electron-transport enzyme	Deficient energy (ATP) production, altered nerve conduction, myopathy, ataxia, seizures

Adapted from (Pena *et al.*, 1999)

2 Physiological copper homeostasis

The extensive early literature on the physiology of copper can now begin to be interpreted given the recent discoveries of the molecular components of the copper homeostatic mechanisms. Here we present only a summary of the overall process of copper transport, for more detailed information, the early work is well summarized in a number of reviews (Evans 1973; Linder 1991; Danks 1995). More recently, reviews incorporating the molecular advances have appeared (Vulpe and Packman 1995; Pena et al. 1999; Harris 2000).