Progress in Neurobiology 116 (2014) 33–57

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Metabolism and functions of copper in brain

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ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form 8 January 2014
Accepted 8 January 2014
Available online 17 January 2014

Keywords:
Astrocytes
Brain
Copper
Neurodegeneration
Transport

ABSTRACT

Copper is an important trace element that is required for essential enzymes. However, due to its redox activity, copper can also lead to the generation of toxic reactive oxygen species. Therefore, cellular uptake, storage as well as export of copper have to be tightly regulated in order to guarantee sufficient copper supply for the synthesis of copper-containing enzymes but also to prevent copper-induced oxidative stress. In brain, copper is of importance for normal development. In addition, both copper deficiency as well as excess of copper can seriously affect brain functions. Therefore, this organ possesses ample mechanisms to regulate its copper metabolism. In brain, astrocytes are considered as important regulators of copper homeostasis. Impairments of homeostatic mechanisms in brain copper metabolism have been associated with neurodegeneration in human disorders such as Menkes disease, Wilson's disease and Alzheimer's disease. This review article will summarize the biological functions of copper in the brain and will describe the current knowledge on the mechanisms involved in copper transport, storage and export of brain cells. The role of copper in diseases that have been connected with disturbances in brain copper homeostasis will also be discussed.

Contents

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; APP, amyloid precursor protein; Atox 1, human antioxidant protein 1; Atx1, antioxidant protein 1; BBB, blood–brain barrier; BCB, blood–cerebrospinal fluid barrier; CCS, copper chaperone for superoxide dismutase; Cp, ceruloplasmin; CNS, central nervous system; CSF, cerebrospinal fluid; Ctr, copper transporter; DβM, dopamine-β-monoxygenase; DMT1, divalent metal transporter 1; DOPA, 3,4-dihydroxyphenylalanine; EPR, electron paramagnetic resonance; GABA, γ-aminobutyric acid; GPI, glycosylphosphatidylinositol; GSH, glutathione; hCtr1, human copper transporter 1; HD, Huntington's disease; Hif-1α, hypoxia-inducible factor 1α; Hspa5, heat shock 70 kDa protein 5; IMS, intermembrane space; LA-ICP-MS, laser ablation inductively coupled plasma mass spectroscopy; LOX, lysyl oxidase; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MBD, metal binding domain; MT, metallothionein; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; PAM, peptidylglycine α-amidating monoxygenase; PD, Parkinson's disease; PINA, pineal gland night-specific ATPase; PLC-PKC, phospholipase C-protein kinase C; PrP, prion protein; PrP^{Sc}, pathogenic form of the prion protein; ROS, reactive oxygen species; SOD, superoxide dismutase; TGN, trans-Golgi network; ZIP, ZRT-/IRT-like protein.

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http://dx.doi.org/10.1016/j.pneurobio.2014.01.002

1. Introduction

Copper is an indispensable element for all organisms that have an oxidative metabolism. Copper is after iron and zinc the third most abundant essential transition metal in human liver (Lewinska-Preis et al., 2011). Although some compounds exist with copper in the oxidation states Cu^{3+} and Cu^{4+}, copper biochemistry is largely dominated by Cu^{+} and Cu^{2+} compounds, as these ions form numerous complexes with both organic and inorganic ligands. The soft Cu^{+} ion prefers ligands that have large polarizable electron clouds, such as sulfur ligands or unsaturated nitrogen donors. Such ligands usually exert coordination numbers from two to four with linear, trigonal or tetrahedral coordination, while the hard Cu^{2+} ion prefers sp^3 hybridized nitrogen and oxygen ligands (Crichton and Pierre, 2001; Kaim and Rall, 1996; Rubino and Franz, 2012; Tisato et al., 2010; Wadas et al., 2007). The reduction potential of the Cu^{2+}/Cu^{+} redox pair varies dramatically depending on the ligand environment and the pH. For example, the one electron oxidation of various Cu^{+}-complexes toward dioxygen has been reported to vary between −1.5 and +1.3 V (Tisato et al., 2010), while in copper proteins the reduction potential for Cu^{2+}/Cu^{+} ranges from +0.32 V to +0.78 V (Rubino and Franz, 2012).

The brain concentrates heavy metals including copper for metabolic use (Bush, 2000). Copper is of great importance for the normal development and function of the brain. As a cofactor of several enzymes and/or as structural component, copper is involved in many physiological pathways in the brain. This review will summarize the functions of copper in the brain for various biochemical pathways and will describe the current knowledge on the copper homeostasis by addressing copper transport, storage and export in brain cells. Finally, disturbances in the copper homeostasis that have been connected with neurodegenerative disorders will be discussed.

2. Importance of copper for brain function

Copper is utilized in the brain for general metabolic as well as for more brain specific functions (Lutsenko et al., 2010). Copper is an essential cofactor and/or a structural component of a number of important enzymes (Scheiber and Dringen, 2013) which are involved in redox reactions (Kaim and Rall, 1996; Rubino and Franz, 2012). The relatively high reduction potential of the Cu^{2+}/Cu^{+} system enables many of the copper enzymes to directly oxidize their substrates, for example superoxide by superoxide dismutase and catechols by tyrosinase (Tisato et al., 2010). Copper-dependent enzymes participate in biological processes such as energy metabolism (cytochrome *c* oxidase), antioxidative defense (Zn,Cu-containing superoxide dismutases), iron metabolism (ceruloplasmin), neurotransmitter synthesis (dopamine-β-monoxygenase) and neuropeptide synthesis (peptidylglycine-α-amidating enzyme).

2.1. Energy metabolism

The brain is one of the most energy-demanding tissues of the body (Rossi et al., 2004). Most of this energy is required for active ion transport processes (Vergun et al., 2007). Since 95% of total ATP in the brain is estimated to be generated in mitochondria (Vergun et al., 2007), mitochondrial efficiency is essential for brain function. The final step of the electron transfer in the mitochondrial respiratory chain, the oxidation of reduced cytochrome *c* by dioxygen, is catalyzed by cytochrome *c* oxidase, also known as complex IV of the respiratory chain (Diaz, 2010; Ferguson-Miller and Babcock, 1996; Hatefi, 1985; Tsukihara et al., 1996). This protein is a member of the super-family of heme-copper containing oxidases (Ferguson-Miller and Babcock, 1996; Popovic et al., 2010; Stiburek et al., 2009). Mammalian cytochrome *c* oxidase is a multimeric protein complex consisting of 13 subunits, encoded by both the mitochondrial and nuclear genome (Hatefi, 1985; Leary et al., 2009b; Stiburek and Zeman, 2010; Tsukihara et al., 1995, 1996). The mitochondria encoded subunits of cytochrome *c* oxidase, Cox1, Cox2 and Cox3, constitute the catalytic core at which the dioxygen reduction and proton translocation take place (Diaz, 2010; Ferguson-Miller and Babcock, 1996; Hamza and Gitlin, 2002; Hatefi, 1985). Cox1 contains two heme moieties (hemes *a* and a_3) and one copper ion (Cu_B; Hatefi, 1985; Tsukihara et al., 1995, 1996). Cox2 contains a binuclear copper center (Cu_A) which serves as the initial electron acceptor from cytochrome *c* (Tsukihara et al., 1995, 1996). During dioxygen reduction electrons derived from cytochrome *c* are transferred from the Cu_A center first to heme *a* and then to the site of dioxygen binding and reduction which is a binuclear center consisting of heme a_3 and Cu_B (Ferguson-Miller and Babcock, 1996; Tsukihara et al., 1995, 1996).

Cytochrome *c* oxidase deficiency is one of the most common causes of respiratory chain defects in humans (Borisov, 2002; Diaz, 2010; Hamza and Gitlin, 2002). Human cytochrome *c* oxidase deficiency manifests as wide variety of disorders with distinct clinical phenotypes resulting from a number of unique genetic abnormalities (Borisov, 2002; Diaz, 2010; Hamza and Gitlin, 2002). Pathological features range from metabolic acidosis, weakness and cardiomyopathy to neurodegeneration (Borisov, 2002; Diaz, 2010; Hamza and Gitlin, 2002). Cytochrome *c* oxidase deficiency rarely