Neurochemistry International 62 (2013) 556–565

Contents lists available at SciVerse ScienceDirect

Neurochemistry International

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

Review

Astrocyte functions in the copper homeostasis of the brain

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ARTICLE INFO

Article history:
Available online 8 September 2012

Keywords:
Astroglia
Metallothioneins
Toxicity
Neurodegeneration
Oxidative stress
Transport

ABSTRACT

Copper is an essential element that is required for a variety of important cellular functions. Since not only copper deficiency but also excess of copper can seriously affect cellular functions, the cellular copper metabolism is tightly regulated. In brain, astrocytes appear to play a pivotal role in the copper metabolism. With their strategically important localization between capillary endothelial cells and neuronal structures they are ideally positioned to transport copper from the blood–brain barrier to parenchymal brain cells. Accordingly, astrocytes have the capacity to efficiently take up, store and to export copper. Cultured astrocytes appear to be remarkably resistant against copper-induced toxicity. However, copper exposure can lead to profound alterations in the metabolism of these cells. This article will summarize the current knowledge on the copper metabolism of astrocytes, will describe copper-induced alterations in the glucose and glutathione metabolism of astrocytes and will address the potential role of astrocytes in the copper metabolism of the brain in diseases that have been connected with disturbances in brain copper homeostasis.

1. Introduction

Copper is an essential cofactor and/or a structural component of a number of enzymes (Table 1). Copper-dependent enzymes are involved in redox reactions (Kaim and Rall, 1996) and participate in important biochemical pathways including energy metabolism (e.g., cytochrome c oxidase), antioxidative defense (e.g., Cu/Zn superoxide dismutase) and iron metabolism (e.g., ceruloplasmin). However, also cellular excess of copper can be harmful for cells, since copper can inhibit protein functions (Letelier et al., 2005) and can catalyze the production of hydroxyl radicals in a Fenton-like reaction (Halliwell and Gutteridge, 2007; Uriu-Adams and Keen, 2005), thereby inducing oxidative stress, damage of cellular components and finally cell death.

Since both copper deficiency and excess can seriously affect cellular functions, the copper homeostasis of cells and tissues is tightly regulated by a complex network of complementary mechanisms (Lutsenko, 2010). The brain concentrates copper for metabolic use (Bush, 2000) to contents that range in the human brain from 3.1 to 5.1 μg/g wet weight (Lech and Sadlik, 2007; Rahil-Khazen et al., 2002). However, copper is unevenly distributed in the brain with copper contents that are higher in grey matter than in white matter (Becker et al., 2005; Dobrowolska et al., 2008). Alterations of copper homeostasis in brain have been connected with aging (Serpa et al., 2008) as well as with neurodegenerative diseases (Bush, 2012; Gaggelli et al., 2006; Rivera-Mancia et al., 2010).

In the brain, astrocytes fulfill a range of important and essential functions (Parpura et al., 2012; Sofroniew and Vinters, 2010). These include the extracellular ion homeostasis, metabolic supply to neurons, the maintenance of the blood–brain barrier (BBB) as well as the modulation of synaptic transmission and synaptic plasticity (Parpura et al., 2012; Sofroniew and Vinters, 2010). Besides their important role in normal brain physiology, astrocytes have been discussed to be involved in pathological processes and in the etiology of neurological diseases such as Alzheimer disease and Parkinson's disease (Halliday and Stevens, 2011; Parpura et al., 2012). For example accumulation of α-synuclein in astrocytes has been shown to cause severe astrogliosis and to result in microglial activation and subsequent loss of dopaminergic and motor neurons (Gu et al., 2010). This process has been considered as an early event in the progression of Parkinson's disease (Halliday and Stevens, 2011).

Astrocytes have a strategically important location in the brain, being in close contact to both neurons and to endothelial cells of

Abbreviations: BBB, blood–brain barrier; CCS, copper chaperone for copper/zinc superoxide dismutase; Ctr1, copper transporter receptor 1; DMT1, divalent metal transporter 1; GSH, glutathione; Hspa5, heat shock 70 kDa protein 5; MTs, metallothioneins; Prp, prion protein; ROS, reactive oxygen species; ZIP, Zrt/IRT-like protein.

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http://dx.doi.org/10.1016/j.neuint.2012.08.017

Table 1
Mammalian copper-dependent enzymes.

Enzyme	Function	Selected review articles	Articles describing the presence of the enzymes in brain
Cytochrome *c* oxidase	Oxidative phosphorylation	Ferguson-Miller and Babcock (1996)	Hevner and Wong-Riley (1989)
Cu/Zn superoxide dismutase	Superoxide detoxification	Miao and St Clair (2009)	Takashima et al. (1990)
Ceruloplasmin	Ferroxidase	Healy and Tipton (2007)	Chang et al. (2005) Klomp and Gitlin (1996)
Lysyl oxidase	Crosslinking of collagen and elastin	Lucero and Kagan (2006)	Li et al. (2004)
Tyrosinase	Melanin synthesis	Olivares and Solano (2009)	Greggio et al. (2005) Tief et al. (1998)
Dopamin-β-monoxygenase	Noradrenaline synthesis	Klinman (2006)	Geffen et al. (1969) Stewart and Klinman (1988)
Peptidylglycine α-amidating enzyme	Activation of peptide hormones	Bousquet-Moore et al. (2010)	Rhodes et al. (1990)
Copper amine oxidase	Deamination of amines	Brazeau et al. (2004)	Jiang et al. (2008) Unzeta et al. (2007)

Table 2
Proteins and peptides involved in the copper metabolism of astrocytes.

Protein	Function	Selected review articles	Articles describing the presence of the proteins in astrocytes
Copper transporter receptor 1 (Ctr1)	Copper uptake	Gupta and Lutsenko (2009)	Scheiber et al. (2010a,b)
Divalent metal transporter 1 (DMT1)	Copper uptake	Arredondo et al. (2003)	Burdo et al. (2001) Jeong and David (2003)
Copper chaperone for superoxide dismutase (CCS)	Intracellular copper trafficking	Robinson and Winge (2010)	Rothstein et al. (1999)
ATOX1	Intracellular copper trafficking	Robinson and Winge (2010)	
Cox17	Intracellular copper trafficking	Robinson and Winge (2010)	
Glutathione (GSH)	Storage and detoxification	Schmidt and Dringen (2012)	Dringen and Hamprecht (1998) Scheiber and Dringen (2011a)
Metallothioneins (MTs)	Storage and detoxification	Vasak and Meloni (2011)	Aschner (1997) Luther et al. (2012)
ATP7A	Copper export	Gupta and Lutsenko (2009)	Scheiber et al. (2012) Niciu et al. (2007) Barnes et al. (2005)

brain capillaries. In fact, astrocytic end-feet cover almost completely the brain capillaries (Mathiisen et al., 2010). Thus, astrocytes are the first brain parenchymal cells that encounter metal ions that cross the BBB. Accordingly, astrocytes are equipped with the required machinery that allows them to function as metal depots and as regulators for the distribution of essential metals to other types of brain cells (Dringen et al., 2007; Tiffany-Castiglioni et al., 2001, 2011). For example, astrocytes are considered to protect neurons against the toxicity induced by metals such as mercury, iron, aluminum and silver by rapid uptake and potential storage of the metal ions (Luther et al., 2011, 2012; Morken et al., 2005; Oshiro et al., 2000). On the other hand, astrocytes are considered as key regulators of the iron metabolism of the brain. These cells efficiently accumulate and store iron (Hoepken et al., 2004; Jeong and David, 2003; Tulpule et al., 2010) and have the capacity to export iron in a process that involves ferroportin and ceruloplasmin (Jeong and David, 2003, 2006). The importance of this astrocytic iron supply function becomes evident by the inherited neurodegenerative disorder aceruloplasminemia which is characterized by loss of neurons and strong iron accumulation in astrocytes (Kaneko et al., 2012; Kono, 2012).

Multiple evidence suggests that astrocytes play an important role in the copper homeostasis of the brain. Within the brain copper has histochemically been shown to be concentrated in astrocytes and it has been suggested already decades ago that these cells may regulate the copper supply to neurons (Kodama, 1993; Kodama et al., 1991; Szerdahelyi and Kasa, 1986). In the North Ronaldsay sheep, an animal model for copper toxicosis, an elevated brain copper content was accompanied by copper accumulation in astrocytes and by a strong astrocytic immunoreactivity for metal storing metallothioneins (MTs; Haywood et al., 2008). In addition, astrocytes in culture have been reported to take up copper more efficiently than cultured neurons and to protect neurons from copper toxicity (Brown, 2004). This protection of neurons against copper toxicity is likely to involve the removal of copper by uptake into astrocytes. In addition, astrocytes release compounds that prevent the copper-mediated removal of extracellular glutathione (GSH; Pope et al., 2008). Since trafficking of GSH from astrocytes to neurons is essential to maintain neuronal GSH levels (Dringen et al., 1999b; Hirrlinger and Dringen, 2010), this stabilization of extracellular GSH may also have neuroprotective functions (Pope et al., 2008).

Mechanisms involved in copper metabolism of brain astrocytes have frequently been studied on cell culture models. Most of the available data have been obtained by using primary astrocyte cultures (Brown, 2004; Qian et al., 2012; Scheiber et al., 2010a) that are highly enriched in astrocytes but contain also low numbers of other types of glial cells (Gutterer et al., 1999; Hansson and Thorlin, 1999; Saura, 2007). In addition, copper metabolism has been studied on tumor cell lines with glial properties (Ferretti et al., 2003; Merker et al., 2005; Qian et al., 2005, 2012). However, since at least primary astrocyte cultures and the C6 glioma cell line differ markedly in their copper uptake properties (data not shown; Qian et al., 2012) this review will focus predominately on data obtained from primary astrocyte cultures as a model system.

This article gives an overview on the current knowledge on the mechanisms and proteins involved in the uptake, storage and export of copper by astrocytes (Table 2). In addition, copper-mediated alterations in the basic metabolism of astrocytes will be discussed. Finally, we will address a possible role of the astrocytic copper metabolism and copper-induced alterations of astrocytic metabolism in neurodegenerative processes.