Neurotoxicity of Copper

Felix Bulcke, Ralf Dringen, and Ivo Florin Scheiber

Abstract Copper is an essential trace metal that is required for several important biological processes, however, an excess of copper can be toxic to cells. Therefore, systemic and cellular copper homeostasis is tightly regulated, but dysregulation of copper homeostasis may occur in disease states, resulting either in copper deficiency or copper overload and toxicity. This chapter will give an overview on the biological roles of copper and of the mechanisms involved in copper uptake, storage, and distribution. In addition, we will describe potential mechanisms of the cellular toxicity of copper and copper oxide nanoparticles. Finally, we will summarize the current knowledge on the connection of copper toxicity with neurodegenerative diseases.

Keywords Copper • Nanoparticles • Neurotoxicity • Neurodegenerative disease • Oxidative stress • Brain

Introduction

Copper represents the third most abundant essential transition metal in humans (Lewińska-Preis et al. 2011). After the liver, the brain is the organ containing the highest copper content (Szerdahelyi and Kása 1986). In its function as a cofactor and/or as structural component for several enzymes, copper participates in many physiological pathways, including energy metabolism, antioxidative defense and iron metabolism (Scheiber et al. 2014). Furthermore, copper has been linked to important biological processes including angiogenesis, response to hypoxia and neuromodulation (Scheiber et al. 2014). However, excess of cellular copper above the needs is deleterious. Given the requirement for copper on the one hand and the potential toxicity of copper on the other hand, cells have evolved mechanisms to

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maintain cellular copper concentrations in a proper range. However, in genetic copper dyshomeostasis and in neurodegenerative diseases, these homeostatic mechanisms may fail and as a consequence copper deficiency or copper overload may occur. Following a brief overview on copper homeostasis and the essentiality of copper, this chapter will review the potential mechanisms of copper toxicity and list the neurologic diseases that have been connected to noxious effects of copper. In addition, we will discuss the toxicity of copper nanoparticles.

Brain Copper Content and Spatial Distribution

Total brain copper content has been estimated to be 3.1 μg g^{-1} wet weight in humans (Lech and Sadlik 2007), 5.5 μg g^{-1} wet weight in mice (Waggoner et al. 2000), and 1.0 μg g^{-1} wet weight in rat (Olusola et al. 2004). However, the brain is a heterogeneous organ with anatomically and physiologically different regions which vary in their specific copper contents (Davies et al. 2012; Krebs et al. 2014; Ramos et al. 2014). In humans, by far the highest copper contents are found in locus coeruleus and substantia nigra (Warren et al. 1960; Davies et al. 2012; Krebs et al. 2014), two structures which are rich in neuromelanin, but also areas within the hippocampus are strongly enriched in copper (Dobrowolska et al. 2008). While the copper concentration of the cerebrospinal fluid (CSF) in humans and rodents ranges between 0.2 and 0.5 μM (Stuerenburg 2000; Forte et al. 2004; Strozyk et al. 2009; Fu et al. 2015), the extracellular copper concentration in brain tissue may be higher. At least for the synaptic cleft, copper concentrations of up to 250 μM have been reported (Kardos et al. 1989; Hopt et al. 2003).

Brain copper content and distribution change during development, with age and in neurodegenerative diseases. An increase in copper content with age has been reported for rodents (Maynard et al. 2002; Tarohda et al. 2004; Wang et al. 2010; Fu et al. 2015) and cattle (Zatta et al. 2008), whereas no significant alteration with age was observed for most human brain regions (Loeffler et al. 1996; Davies et al. 2012; Ramos et al. 2014). The copper content in brains of Wilson's disease (WD) patients was shown to be almost eight times that of control brains, with homogeneous copper accumulation in all brain regions (Litwin et al. 2013). Such a nonselective increase of copper throughout the brain was also observed in the ATP7B null mice, a rodent model of Wilson's disease (Boaru et al. 2014). Brain copper contents of Menkes disease (MD) patients (Nooijen et al. 1981; Willemse et al. 1982) and mouse models of MD (Camakaris et al. 1979; Lenartowicz et al. 2015) were found to be lowered to values down to 20% of those found for controls. The amyloid plaques in Alzheimer's disease (AD) brain are strongly enriched in copper (Lovell et al. 1998), while cerebral cortex, frontal cortex, amygdala, and hippocampus were shown to be decreased by up to 50% in copper content (Deibel et al. 1996; Akatsu et al. 2012; James et al. 2012; Rembach et al. 2013). In Parkinson's disease (PD) and incidental Lewy body disease, a reduction by about 50% in copper content of substantia nigra and locus coeruleus has been reported (Ayton et al. 2013; Davies

et al. 2014). Substantial lower copper levels have also been observed in hippocampal tissue from patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (Ristić et al. 2014) and in brains of scrapie-infected mice (Thackray et al. 2002), whereas an increase in copper was shown for the striatum of Huntington's disease (HD) patients (Dexter et al. 1992) and in iron-rich areas of the dentate nucleus of patients suffering from Friedreich's ataxia and spinocerebellar ataxia type 3 (Koeppen et al. 2012).

Copper Homeostasis

Cellular Copper Homeostasis

Many components of the cellular copper homeostasis machinery have been described at the molecular level (Fig. 1). The copper transport receptor (Ctr) 1 is considered as the major entry pathway for copper into mammalian cells (Lee et al. 2002a, b), but other copper uptake systems have also been reported (Lee et al. 2002b; Moriya et al. 2008; Kidane et al. 2012). Further evidence for such alternative transport mechanism was provided by data from cell-specific Ctr1 knockout mice (Nose et al. 2006; Kim et al. 2009). The copper transporter Ctr2 (Bertinato et al. 2008), the divalent metal transporter (DMT) 1 (Arredondo et al. 2003; Espinoza et al. 2012; Monnot et al. 2012; Lin et al. 2015), and anion transporters (Alda and Garay 1990; Zimnicka et al. 2011) have been discussed as possible candidate proteins mediating this alternative transport mechanism (Fig. 1). The accumulation of copper in the cytosol bears the risk of copper toxicity. However, under physiological conditions, the concentration of free copper within the cell is kept very low at around 10^{-18} M (Rae et al. 1999). This low concentration of free copper is maintained by efficient binding of copper to metallothioneins (MTs) and ligands of low molecular mass such as glutathione (GSH) (Scheiber et al. 2014). In addition, mitochondria are likely to contribute to the cellular copper buffering capacity (Cobine et al. 2004; Maxfield et al. 2004; Leary et al. 2009). A group of specialized proteins, termed copper chaperones, shuttle copper to copper-dependent enzymes and to organelles (Fig. 1), thereby protecting it from being scavenged by MTs or GSH. Atox1 transfers Cu^{+} to the N-terminal metal-binding domains of the copper-transporting P-type ATPases ATP7A and ATP7B; the copper chaperone for superoxide dismutase (CCS) facilitates the insertion of copper into superoxide dismutase (SOD) 1, while Cox17, Sco1, Sco2, and Cox11 participate in the insertion of copper ions into mammalian cytochrome c oxidase (Robinson and Winge 2010). In addition, a yet to be identified copper ligand aids in the transport of copper into the mitochondrial matrix (Cobine et al. 2004; Vest et al. 2013). Cellular copper export in mammals relies on the function of two proteins, ATP7A and ATP7B (Fig. 1). These proteins belong to the protein family of P1B-type ATPases that use the energy of ATP hydrolysis to transport heavy metals across cellular membranes

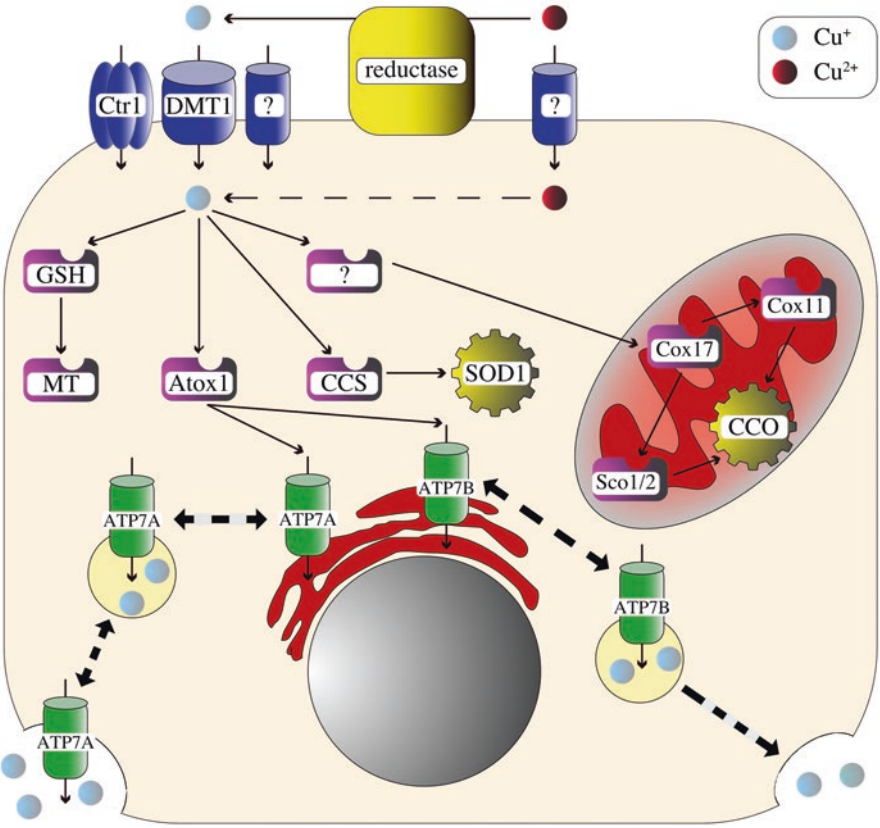

Fig. 1 Mechanism of cellular copper transport. Copper enters cells via the copper transporter Ctr1, DMT 1, and/or yet-unknown transporters. A cuprireductase provides Cu^{+}, the preferred substrate for Ctr1 and DMT1. In cells, accumulated copper is sequestered by GSH or stored in metallothioneins (MT). Copper chaperones shuttle copper to its specific cellular targets. CCS provides copper to SOD1. A yet-unknown copper ligand aids in the transport of copper into the mitochondrial matrix and Cox17, Sco1/Sco2 and Cox11 participate in the insertion of copper into cytochrome c oxidase (CCO). Atox1 delivers copper to the copper-transporting P-type ATPases ATP7A and ATP7B that shuttle copper to the secretory pathway for subsequent incorporation into copper-dependent enzymes and mediate cellular copper efflux

(Arguello et al. 2007). In addition to their critical function in the efflux of cellular copper, ATP7A and ATP7B shuttle copper to the secretory pathway for incorporation into copper-dependent enzymes such as tyrosinase, peptidylglycine-amidating monooxygenase (PAM), dopamine β-monooxygenase (DβM), lysyl oxidase (LOX), and ceruloplasmin (Cp) (Scheiber et al. 2014). In the brain, ATP7A is further required for the release of copper from hippocampal neurons upon NMDA activation (Schlief et al. 2005).

Systemic Copper Homeostasis

Overall balance of systemic copper in the body is achieved by regulation of the rate of uptake of copper in the small intestine and efflux of copper from the liver in the bile (Scheiber et al. 2013). Most dietary copper is absorbed in the small intestine (Linder and Hazegh-Azam 1996), and Ctr1 has been shown to be essential for this process as mice with intestinal-specific knockout of Ctr1 exhibited severe copper deficiency and death by 3 weeks of age due to intestinal block of copper absorption (Nose et al. 2006). While it is clear that Ctr1 is required for copper to be bioavailable (Nose et al. 2006), its function in apical copper entry is still under controversial debate. In most studies, Ctr1 was observed to be localized to the apical surface (Kuo et al. 2006; Nose et al. 2010), but Zimnicka et al. (2007) reported that Ctr1 is located at the basolateral membrane in the enterocytes. Furthermore, enterocytes deficient in Ctr1 hyperaccumulated copper (Nose et al. 2006), suggesting the contribution of other transporters in the transport of copper across the brush border of the intestinal epithelial cells. Indeed, DMT1 (Arredondo et al. 2003; Espinoza et al. 2012) and anion transporters (Zimnicka et al. 2011) have been implicated in this process. The copper efflux protein ATP7A is responsible for the transport of copper across the basolateral surface of intestinal epithelia cells into portal circulation (Scheiber et al. 2013). Increasing dietary copper causes ATP7A in intestinal enterocytes to traffic from the *trans*-Golgi network (TGN) to sub-basolateral membrane vesicles that periodically fuse with the plasma membrane to release copper into the basolateral milieu (Monty et al. 2005; Nyasae et al. 2007). ATP7B is the transporter responsible for efflux of copper from the liver into the bile, the principle pathway for removing excess copper from the body (Scheiber et al. 2013). Excess copper in the hepatocyte stimulates trafficking of this protein from the TGN to vesicles close to the apical membrane of the hepatocyte that abuts the biliary canaliculus (Cater et al. 2006), thus increasing the capacity of rapid copper sequestration from the cytosol and allowing for subsequent excretion of excess copper via exocytosis.

Brain Copper Homeostasis

Brain copper homeostasis is regulated by the brain barrier systems, i.e., the blood-brain barrier (BBB) and blood-CSF barrier (BCB). The main route for copper entry into the brain parenchyma appears to be the BBB (Fig. 2), requiring the combined action of Ctr1 and ATP7A (Choi and Zheng 2009; Monnot et al. 2011; Zheng and Monnot 2012; Fu et al. 2014). Ctr1 is strongly expressed in brain capillary endothelial cells (Kuo et al. 2006) and has been proposed to locate on the luminal side of these cells (Kaler 2011) making it an ideal candidate in regulating copper uptake from the blood. Copper levels in brains of Ctr1-heterozygous knockout mice are reduced to about 50% of that of wild-type animals (Lee et al. 2001) confirming the fundamental role for Ctr1 in the transport of copper across the BBB into the brain.

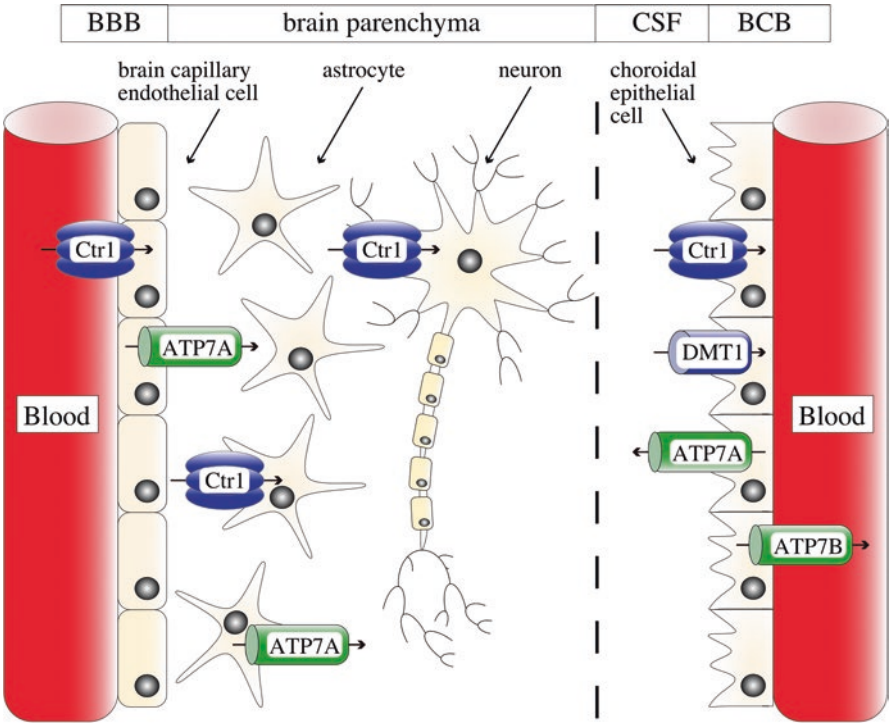

Fig. 2 Brain copper homeostasis. The blood-brain barrier (BBB) appears to be the main route for copper entry into the brain. Brain capillary endothelial cells take up copper from the blood via Ctr1. These cells release copper via ATP7A into the brain parenchyma and copper is subsequently taken up into astrocytes, neurons and other brain cells, most likely predominantly via Ctr1. At least astrocytes release via ATP7A excess of copper into the CSF. The choroid plexus functions in extracting copper from the CSF. Copper taken up via Ctr1 and/or DMT1 into choroidal epithelial cells that constitute the blood-CSF barrier (BCB) is either released into the blood via ATP7B or stored for potential release by ATP7A back into the CSF

The requirement of ATP7A in copper export from brain capillary endothelial cells has been demonstrated in a cell culture model for these cells (Qian et al. 1998) and dysfunction of ATP7A results in hyperaccumulation of copper in brain capillaries of mouse models of Menkes disease (Kodama 1993; Yoshimura et al. 1995). ATP7A mRNA levels in the BBB were found to be about 13 times higher than ATP7B mRNA levels, supporting a predominant role for ATP7A in copper export from brain capillary endothelial cells into brain parenchyma (Fu et al. 2014). Although the transport of copper from blood circulation into the choroid plexus (CP) is faster than into cerebral capillaries, further transport of copper from the CP into the CSF is very slow, virtually prohibiting the passage of copper from blood to CSF (Choi and Zheng 2009; Fu et al. 2014). Moreover, in vitro and in vivo data demonstrated that the direction of BCB in transporting copper is from the CSF to blood (Fig. 2), providing evidence that the BCB's role in CNS copper homeostasis is to remove

copper from the CSF (Monnot et al. 2011). However, the situation might be different in the developing brain for which the BCB has been hypothesized to be the primary route of copper entry (Donsante et al. 2010). Using a choroidal cell model, it was shown that both Ctr1 and DMT1 mediate copper accumulation by choroidal epithelial cells (Monnot et al. 2012; Zheng et al. 2012) although Ctr1 appears to play a much more significant role in transporting Cu into the cells than does DMT1 (Zheng et al. 2012). Both transporters are enriched at the apical membrane of epithelial cells of the CP (Kuo et al. 2006; Wang et al. 2008; Davies et al. 2012; Zheng and Monnot 2012) consistent with the proposed function of the CP in extracting copper from the CSF. In contrast to the BBB, ATP7B mRNA is more abundantly expressed in choroidal epithelial cells than ATP7A. However, data from siRNA knockdown experiments indicates that both Cu-transporting ATPases, ATP7A and ATP7B, contribute to copper transport across the BCB (Fu et al. 2014). Furthermore, upon copper incubation of rat choroid plexus tissue, ATP7B was shown to traffic from a perinuclear location toward the basolateral membrane, whereas ATP7A translocated toward the apical microvilli, suggesting that while ATP7B is responsible for release of copper into the blood, ATP7A is responsible for the efflux of copper from choroidal epithelial cells into the CSF (Fu et al. 2014). Such trafficking behavior of ATP7A and ATP7B in choroidal epithelial cells has been previously hypothesized by Kaler (Kaler 2011) but contrasts the situation reported for other polarized cells (Monty et al. 2005; Llanos et al. 2008; Michalczyk et al. 2008) and to the localization of ATP7A and ATP7B reported for human epithelial cells of the CP (Davies et al. 2012).

Essentiality of Copper

By virtue of its function as cofactor and/or structural component in a number of important enzymes, copper is essential for a variety of biological pathways (Scheiber et al. 2014). 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, a member of the superfamily of heme-copper-containing oxidases (Ferguson-Miller and Babcock 1996). The copper-dependent SODs 1 and 3 contribute to the antioxidative defense by catalyzing the dismutation of superoxide to oxygen and hydrogen peroxide (Perry et al. 2010). The multi-copper oxidase Cp plays an important role in iron homeostasis and thus links copper and iron metabolism (Healy and Tipton 2007). Lysyl oxidase has a crucial role in the formation, maturation, and stabilization of connective tissues by catalyzing the cross-linking of elastin and collagen (Lucero and Kagan 2006). Both DβM and PAM belong to a small class of copper proteins found exclusively in mammals (Klinman 2006). DβM catalyzes the final step in noradrenaline synthesis, the oxidative hydroxylation of dopamine to noradrenaline, and thus plays an important role in the catecholamine metabolism (Timmers et al. 2004). PAM exclusively catalyzes the C-terminal α-amidation of propeptides, a posttranslational modification essential for the

bioactivity of diverse physiological regulators, including peptide hormones, neurotransmitters, and growth factors (Bousquet-Moore et al. 2010b). Tyrosinase is the key enzyme in the biogenesis of melanin pigments. Among others, tyrosinase catalyzes the hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), the rate-limiting step in the biosynthesis of melanins and dopamine, and its subsequent oxidation to DOPA quinone (Olivares and Solano 2009). Primary and secondary copper amine oxidases regulate biogenic amine levels by catalyzing their oxidative deamination (Klinman 1996).

In addition to its requirement for enzymes, a growing body of evidence indicates a role for copper in biological processes such as coagulation (Wakabayashi et al. 2001), angiogenesis (Urso and Maffia 2015), response to hypoxia (Feng et al. 2009), nonclassical secretion (Prudovsky et al. 2008), and neuromodulation (Gaier et al. 2013). Synaptosomes and primary hippocampal neurons have been shown to release copper following depolarization (Kardos et al. 1989; Hopt et al. 2003; Schlief et al. 2005) in concentrations sufficient to modulate excitatory and inhibitory neurotransmission (Gaier et al. 2013; Scheiber et al. 2014). Several of the neuromodulatory functions of copper appear to be directly linked to interactions of copper with receptors, but copper may exert its neuromodulatory functions also by altering intracellular signaling pathways (Gaier et al. 2013; Scheiber et al. 2014). The exact role of copper in synaptic physiology remains to be elucidated (for review, see Gaier et al. 2013). However, synaptically released endogenous copper and exogenously applied copper protect primary hippocampal neurons against NMDA-mediated excitotoxic cell death (Schlief and Gitlin 2006) in a process that involves the cellular prion protein (Gasperini et al. 2015). While an inhibitory effect of copper on long-term potentiation (LTP) has been demonstrated using hippocampus slices that had been exposed to exogenous copper (Doreulee et al. 1997; Salazar-Weber and Smith 2011) and hippocampal slices of rats that had been fed a high-copper diet (Goldschmith et al. 2005; Leiva et al. 2009), copper has been shown to be required for amygdalar LTP (Gaier et al. 2014a, b).

The essentiality of copper is best illustrated by MD, a rare, X-linked recessive disorder caused by genetic defects in the copper-transporting ATPase ATP7A that manifests with clinical symptoms, including severe progressive neurological degeneration, increased seizure frequency, connective tissue abnormalities, muscular hypotonia, hypothermia, and abnormalities of the skin and hair (Kaler 2011; Kodama et al. 2011). As ATP7A is required for the transport of copper across the basolateral surface of intestinal epithelia cells into portal circulation, loss of function of ATP7A leads to failure of copper absorption in the intestine and hence to a systemic copper deficiency (Kodama et al. 2011). Treatment with parental copper can improve neurological outcomes when initiated in the neonatal period and the BBB is immature, but proves ineffective when initiated at later age due to the essential role of ATP7A for copper transport across the BBB (Kaler 2011; Kodama et al. 2011). Many of the clinical symptoms of MD can be ascribed to a decrease in the activities of secreted copper-dependent enzymes that rely on the function of ATP7A to receive their copper (Kaler 2011; Kodama et al. 2011). Decreased PAM activity and the subsequent lack of α-amidated peptides are thought to contribute to the

neurodevelopmental delay and increased seizure frequency associated with MD (Bousquet-Moore et al. 2010a; Kaler 2011). Partial deficiency of DβM accounts for the elevated dopamine to noradrenaline ratio in plasma and CSF of MD patients (Kaler 1998). Hypopigmentation of the skin and hair is a consequence from reduced tyrosinase activity and lowered LOX activity is responsible for bone and connective tissue abnormalities (Kaler 2011; Kodama et al. 2011). However, low CCO activity as a consequence of impaired transport of copper into the brain is likely to be the major cause of the severe neurodegeneration associated with MD (Kaler 2013; Scheiber et al. 2014). In support of this view, a mouse model ($Atp7a^{Nes}$) in which the Atp7a gene was selective deleted in neural cells showed normal to slightly elevated brain copper levels and no signs of Menkes-like degenerative neuropathology and early mortality (Hodgkinson et al. 2015). Nevertheless, ATP7A has been shown to have a critical role in the availability of an NMDA receptor-dependent releasable pool of copper in primary hippocampal neurons (Schlief et al. 2005), which has been shown to protect these cells against NMDA-mediated excitotoxic cell death (Schlief et al. 2006). Failure of this copper-dependent neuroprotective pathway in MD may contribute to the extensive neurodegeneration seen in this fatal disease (Schlief et al. 2006; Schlief and Gitlin 2006; Hodgkinson et al. 2015).

Toxicity of Copper

Copper toxicity in individuals without genetic susceptibility is rare (de Romaña et al. 2011). Acute copper toxicity has been described for individuals that accidentally or with suicidal intention ingested high doses of copper (Franchitto et al. 2008). For copper doses up to 1 gram, gastrointestinal symptoms predominate. Ingestion of higher copper doses may result in nausea, vomiting, headache, diarrhea, hemolytic anemia, gastrointestinal hemorrhage, liver and kidney failure and even death may occur (Franchitto et al. 2008). Chronic copper toxicity is a feature of WD, Indian childhood cirrhosis, and idiopathic chronic toxicosis that originate from genetic defects affecting copper metabolism (Scheiber et al. 2013). In addition, copper may contribute as a noxious metal to the pathology of neurodegenerative disorders, including AD, PD, and HD (Scheiber et al. 2014).

Mechanisms of Copper Toxicity

Oxidative Mechanisms

Copper toxicity is in large part a consequence of the redox activity of copper. Copper can easily cycle between the reduced Cu(I) and the oxidized Cu(II) oxidation state, allowing it to facilitate redox reactions and to coordinate a large variety of ligands (Liu et al. 2014). This feature is utilized by most of the copper-dependent enzymes

that employ copper as a cofactor in fundamental redox reactions (Liu et al. 2014). However, the redox nature that makes copper biologically useful also renders it potentially toxic. Redox cycling of copper in the presence of superoxide or reducing agents such as ascorbic acid or GSH may catalyze the generation of highly reactive hydroxyl radicals from hydrogen peroxide via the Haber-Weiss cycle (Gunther et al. 1995). The hydroxyl radical, being the most powerful oxidizing radical likely to arise in biological systems, is capable of initiating oxidative damage by abstracting the hydrogen from an amino-bearing carbon to form a carbon-centered protein radical or from an unsaturated fatty acid to form a lipid radical and by inducing DNA strand breaks and oxidation of bases (Gaetke et al. 2014). In addition, copper ions are capable of accelerating lipid peroxidation by splitting lipid hydroperoxides in a reaction analogous to the Fenton reaction, giving alkoxyl and peroxyl radicals thereby propagating the chain reaction (Halliwell 2006).

Mitochondria are major targets for copper-induced oxidative damage. Ultrastructural changes of liver mitochondria in WD patients; in the Long-Evans Cinnamon (LEC) rat, a rat model of WD; and in rats with dietary copper overload (Sokol et al. 1990; Zischka et al. 2011; Fanni et al. 2014) are accompanied by functional impairment of enzymes of mitochondrial respiration (Sokol et al. 1993; Gu et al. 2000; Zischka et al. 2011). Altered activities of respiratory chain enzyme complexes similar to that found in the liver have been observed in brain tissue of ATP7B$^{-/-}$ mice (Sauer et al. 2011). Treatment of cultured hepatocytes mixed neuronal/glial cultures or neuroblastoma cultures with copper was shown to inhibit mitochondrial pyruvate and α-ketoglutarate dehydrogenase complexes, which was attributed to mitochondrial ROS formation (Sheline and Choi 2004; Arciello et al. 2005). As markers of lipid peroxidation are elevated in hepatocyte mitochondria of WD patients, animal models of WD and rats with dietary copper overload, oxidative membrane damage is likely to contribute to the mitochondrial alterations observed under these copper-overload conditions (Sokol et al. 1990, 1994; Zischka et al. 2011). In addition, increased levels of phosphatidic acid and phosphatidyl hydroxyl acetone have been observed in liver mitochondria of ATP7B$^{-/-}$ mice (Yurkova et al. 2011), indicative of ROS-mediated fragmentation of mitochondrial cardiolipin (Yurkova et al. 2008). Cardiolipin is a phospholipid crucial for integrity and function of the mitochondrial inner membrane and oxidation of cardiolipin has been shown to impair oxidative phosphorylation and to cause induction of apoptosis (Hauck and Bernlohr 2016). The induction of the mitochondrial permeability transition as a consequence of copper-mediated oxidative stress was observed in primary hepatocytes (Roy et al. 2009) and primary astrocytes, but not in primary neurons (Reddy et al. 2008). Mitochondrial permeability transition results in increased permeability of the inner mitochondrial membrane leading to cell death via apoptosis and/or necrosis (Javadov and Kuznetsov 2013).

Extensive genome damage is a common feature of metal-overload conditions, including many neurological disorders, in particular base modifications and strand breaks (Hegde et al. 2011; Mitra et al. 2014). The induction of oxidative DNA damage by copper and various copper complexes has been demonstrated in vitro with isolated DNA (Sagripanti and Kraemer 1989; Tkeshelashvili et al. 1991) and

cultured mammalian cell cultures (Ma et al. 1998; Alimba et al. 2016) as well as in vivo (Prá et al. 2008; Georgieva et al. 2013). Copper is thought to exert its genotoxic effect via a site-specific mechanism that involves the generation of singlet oxygen and/or hydroxyl radicals bound to or in close proximity of high-affinity copper-binding sites on double-stranded DNA rather than via the generation of free hydroxyl radicals (Sagripanti and Kraemer 1989; Tkeshelashvili et al. 1991; Frelon et al. 2003). Facilitation of autoxidation of catecholamines such as adrenaline, L-DOPA, dopamine, and 6-hydroxydopamine by copper results not only in an increased production of superoxide (Halliwell 2006), but complexes resulting from catecholamine oxidation products and copper also oxidatively damage DNA (Lévay et al. 1997; Spencer et al. 2011). This observation has been used to explain the selective copper neurotoxicity in neurodegenerative diseases, in particular PD (Spencer et al. 2011).

The oxidative DNA damage exerted by copper and/or copper-induced oxidative stress may lead to activation of the tumor suppressor protein p53 (Phatak and Muller 2015) which in turn can trigger apoptosis by transcriptionally activating or repressing the expression of a panel of pro- and antiapoptotic proteins or by direct action at the mitochondria (Wang et al. 2014). Indeed, elevated p53 mRNA and protein levels and nuclear translocation of p53 have been shown in liver cells and neurons upon copper exposure (Strand et al. 1998; Narayanan et al. 2001; VanLandingham et al. 2002). A supporting role of p53 in copper-induced cell death has been demonstrated for neurons and liver cells deficient or mutated in p53 which are more resistant to the toxic effect of copper (Strand et al. 1998; VanLandingham et al. 2002). The induction of apoptosis in hepatocytes in response to copper has further been shown to involve the activation of the endogenous CD95 system (Strand et al. 1998), a downstream effector of p53-dependent apoptosis (Haupt et al. 2003), and the activation of acid sphingomyelinase and subsequent release of ceramide (Lang et al. 2007) by copper-induced ROS. As the induction of apoptosis via the CD95 system in hepatocytes has been shown to require the activation of acid sphingomyelinase in vivo (Kirschnek et al. 2000), copper may stimulate acid sphingomyelinase in these cells at least in part through the endogenous CD95 system (Lang et al. 2007). However, in erythrocytes, copper induced phosphatidylserine exposure and death via leukocyte-secreted acid sphingomyelinase, suggesting that ceramide might also be involved in CD95-independent pathways leading to hepatocyte and erythrocyte death after copper treatment (Lang et al. 2007).

Binding to Biomolecules

Although copper toxicity is ascribed in large part as a consequence to copper-induced oxidative stress, direct binding of copper to proteins should be considered. In this regard, copper has been shown to bind to the X-linked inhibitor of apoptosis (XIAP), an antiapoptotic protein that directly binds to and inhibits specific caspases, thereby inducing a conformational change in the protein as well as a decrease in its half-life (Mufti et al. 2006). These two changes make the cell more susceptible to

apoptotic stimuli and may contribute to the pathophysiology of copper toxicosis syndromes (Mufti et al. 2007). In addition, copper may nonspecifically bind to thiol and amino groups in proteins unrelated to copper metabolism, thereby altering protein structure and modifying their biological functions (Letelier et al. 2005). Binding of copper has been shown to inhibit enzymatic activities of the cytochrome P450 oxidative system, GSH transferases, and lactate dehydrogenase (Letelier et al. 2005, 2006; Pamp et al. 2005). Noncompetitive inhibition of Na^+/K^+-ATPase from rat brain synaptic plasma membranes (Vasić et al. 1999; Krstić et al. 2005; Nedeljković and Horvat 2007) and rabbit kidney (Li et al. 1996) by copper most likely occurs via binding of copper to protein sulfhydryl groups (Vujisić et al. 2004). Na^+/K^+-ATPase is concentrated in the synaptic membranes where it mediates potassium uptake and sodium release, which are required to restore ionic equilibria after the passage of nervous impulse (de Lores Arnaiz and Ordieres 2014). Consequently, inhibition of Na^+/K^+-ATPase will lead to diverse alterations of neuronal behavior (de Lores Arnaiz and Ordieres 2014). Copper binding to proteins involved in DNA repair may contribute to copper-induced DNA damage. Copper has been shown to inhibit the activities of the DNA glycosylases NEIL1 and NEIL2 by forming stable complexes with these proteins (Hegde et al. 2010) and to inhibit both phosphatase and kinase activities of the enzyme polynucleotide kinase 3′-phosphatase (PNKP) that is responsible for preparing nicked DNA for ligation (Whiteside et al. 2010). Copper has further been shown to strongly inhibit DNA-binding affinity of the DNA nick-sensor poly(ADP-ribose)polymerase-1 (PARP-1) and H_2O_2-induced poly(ADP-ribosyl)ation in HeLa S3 cells (Schwerdtle et al. 2007). As binding to DNA lesions and the activity of PARP-1 depends on three zinc finger domains (Eustermann et al. 2011), copper may exert its inhibitory effect by displacing zinc and/or by oxidation of the cysteines complexing zinc in these zinc finger structure (Schwerdtle et al. 2007).

Alteration of gene expression and metabolic pathways may also contribute to copper toxicity. Utilizing the ATB7B$^{-/-}$ mice, an animal model for WD, Huster et al. (2007) provided evidence that despite significant copper accumulation, copper-mediated oxidative stress does not play a major role at early stages of the disease. Instead, in presymptomatic ATB7B$^{-/-}$ mice, copper overload was shown to have a distinct and selective effect on liver gene expression and metabolism: Accumulated copper selectively upregulated the molecular machinery associated with cell cycle and chromatin structure and downregulated lipid metabolism (Huster et al. 2007). In fact, transcripts of genes involved in lipid metabolism remain significantly downregulated in ATP7B$^{-/-}$ mice liver at all stages of WD (Ralle et al. 2010). Transcripts of enzymes involved in key steps of cholesterol biosynthesis were found to be most affected and accompanied by a marked decrease in liver cholesterol and VLDL cholesterol in serum (Huster et al. 2007; Ralle et al. 2010). Furthermore, severe dysregulation of sterol metabolism was observed in brains of ATP7B$^{-/-}$ mice (Sauer et al. 2011). The mechanism through which copper induces its effects on gene expression is not yet fully revealed. However, analysis of downregulated signaling pathways revealed a significant involvement of specific nuclear receptors (Burkhead et al. 2011). Indeed, NR3C1/glucocorticoid receptor (GR) and NR1H4/farnesoid X

receptor (FXR), two key nuclear receptors with functions in lipid metabolism, are less abundant in nuclei of ATP7B$^{-/-}$ hepatocytes (Wilmarth et al. 2012). Also nuclear receptor target gene expression and activity are impaired in HepG2 cells treated with copper, livers from ATP7B$^{-/-}$ mice, and hepatic autopsy samples of WD patients (Wooton-Kee et al. 2015). Recent evidence suggests that copper directly decreases nuclear receptor function by competing with zinc for occupancy of the DNA-binding zinc finger domains (Wooton-Kee et al. 2015). The selective effects of copper on gene expression may be explained by differences in zinc finger coordination among different zinc-containing transcription factors that may result in a spectrum of susceptibility to copper interaction with the zinc finger proteins (Wooton-Kee et al. 2015).

Increasing evidence suggests a neuromodulatory function of copper (Gaier et al. 2013; Scheiber et al. 2014). Several of the neuromodulatory functions of copper appear to be linked to its effects on voltage-gated ion channels and synaptic receptors, but copper may exert its neuromodulatory functions also by altering intracellular signaling pathways in neurons (Gaier et al. 2013; Scheiber et al. 2014). Thus, copper neurotoxicity may be in part a consequence of excess copper adversely affecting synaptic transmission and functions.

Neurotoxicity of Copper

A number of neurodegenerative disorders have been connected with disturbances in copper homeostasis in brain (Rivera-Mancia et al. 2010; Scheiber et al. 2014; Bandmann et al. 2015). Here we will only shortly mention the main characteristics of the disorders and will focus more on the evidence presented so far on the roles that copper deprivation or copper excess may play in the pathology of the diseases.

Neurologic Wilson Disease

WD is a rare, inherited autosomal recessive disease of copper metabolism that originates from a genetic defect in the copper-transporting ATPase ATP7B. Impaired ATP7B function in WD results in failure of biliary copper secretion, leading to copper accumulation in the liver, brain and other tissues as well as in failure of loading of Cp with copper (Dusek et al. 2015). The majority of patients with WD present either predominantly hepatic or neuropsychiatric symptoms, the latter occurring in up to 50% of WD patients (Das and Ray 2006). Neurologic symptoms in WD are manifold and include dysarthria, tremor, Parkinsonism, dystonia, ataxia, chorea and cognitive impairments (Lorincz 2010). Ventricular dilatation and generalized atrophy are common neuropathological abnormalities in the WD brain (Meenakshi-Sundaram et al. 2008). Macroscopic structural changes are most consistently observed in the basal ganglia, particularly in the dorsal striatum, but have also been reported for the thalamus, brainstem, and frontal cortex (Brewer and

Yuzbasiyan-Gurkan 1992; Meenakshi-Sundaram et al. 2008). Involvement of the white matter has been considered to be present in at least 10% of cases (Mikol et al. 2005). Copper toxicity is considered as primary cause of the brain damage associated with WD, although other factors, such as decreased Cp oxidase activity and subsequent disturbance of iron metabolism, may also contribute (Dusek et al. 2015). Copper content in brains of WD patients is strongly increased in all brain regions (Litwin et al. 2013) and a fair degree of correlation between the severity of neurodegeneration and cerebral copper content has been reported (Horoupian et al. 1988).

The occurrence of abnormal astrocytes, i.e. Alzheimer type I and II cells and Opalski cells, already in early stages of the disease is a typical neuropathological feature of WD (Mossakowski et al. 1970; Bertrand et al. 2001; Das and Ray 2006). Astrocytes, localized in the brain between neurons and capillary endothelial cells, are considered the first parenchymal cells to encounter metals crossing the BBB (Scheiber and Dringen 2013) and abnormal astrocytes in WD stain strongly for MT and copper (Bertrand et al. 2001; Mikol et al. 2005), suggesting that astrocytes accumulate excess copper, in order to protect neurons from copper toxicity. Such a neuroprotective function of astrocytes has been reported for cultured brain cells (Brown 2004) and is supported by data from the North Ronaldsay sheep, an animal model for copper toxicosis, where an elevated brain copper content was accompanied by increased expression of MT and copper accumulation in astrocytes (Haywood et al. 2008). However, during the course of WD, the storage capacity of astrocytes is likely to get exhausted, leading to astrocyte damage as well as to an increase in extracellular copper in the brain parenchyma. Thus, both impairments of astrocyte functions that are required for normal neuronal function (Parpura et al. 2012) and exposure of neurons to excess copper should be considered to contribute to neuronal death in WD.

Alzheimer Disease

AD is the most common neurodegenerative disease in humans with most of the cases representing the late-onset form that is sporadic with no obvious implication of genetic factors (Prakash et al. 2016). The disease is characterized by a progressive decline and ultimately loss of memory and multiple other cognitive functions along with psychiatric disturbances (Castellani et al. 2010). Aside from age, other risk factors include family history of dementia and genetic and environmental factors (Castellani et al. 2010). The major pathological hallmarks of AD are the presence of extracellular senile plaques, primarily composed of amyloid-β (Aβ) peptides of 40 and 42 residues, and intracellular neurofibrillary tangles, primarily constituted of hyperphosphorylated tau protein (Ballard et al. 2011).

Strong evidence implicates a dyshomeostasis of copper in the etiology of AD, but controversy exists regarding the role of copper in the pathogenic process. While some evidence supports a detrimental role of copper in AD, other studies suggest the opposite. In support of the former, Aβ peptides bind copper with high affinity, and the senile plaques are strongly enriched in copper (Eskici and Axelsen 2012).

Copper has been shown to precipitate Aβ peptides in vitro, and it has been suggested that copper triggers the formation of senile plaques (Roberts et al. 2012). However, with increasing copper:Aβ ratios, the aggregation pathway changes, and the aggregating peptide is diverted into soluble oligomeric forms that are thought to be the most neurotoxic Aβ species (Eskici and Axelsen 2012; Matheou et al. 2015). Although the precise mechanisms by which oligomeric Aβ species exert their toxic effects are unknown, copper may exacerbated the toxicity of such Aβ oligomers through the formation of ROS, as Aβ can mediate the reduction of Cu^{2+} to Cu^{+} (Roberts et al. 2012), by increasing the specific inhibition of cytochrome c oxidase (Crouch et al. 2005) or by enhancing microglial activation (Yu et al. 2015). Moreover, copper has been implicated in tau pathology associated with AD, by stimulating the phosphorylation and aggregation of tau and by enhancing the toxicity of tau aggregates (Du et al. 2014; Voss et al. 2014).

On the contrary, lower copper contents in affected brain regions of AD patients (Loeffler et al. 1996) and mouse models for AD (Bayer et al. 2003) as compared to controls rather argue for a copper deficit contributing to the neurodegeneration in AD. Copper supplementation and administration of Cu(gtsm) as copper source improved the survival and cognitive functions in mouse models of AD (Bayer et al. 2003; Crouch et al. 2009). However, intake of copper had no effect on cognition in patients with mild AD (Kessler et al. 2008). Mechanistically, copper deficiency may exacerbate disease progression by influencing amyloid precursor protein processing and Aβ metabolism (Cater et al. 2008). In addition, copper deficiency may impair the activity of copper-dependent enzymes. In this regard, low activities of cytochrome c oxidase (Maurer et al. 2000) and SOD1 (Marcus et al. 1998) have been reported for the AD brain.

Parkinson Disease

PD is the second most common neurodegenerative disease in humans, with the majority of cases representing idiopathic PD (Thomas and Flint Beal 2007). PD is characterized by a complex motor disorder known as Parkinsonism that manifests with resting tremor, bradykinesia, rigidity and postural instability (Thomas and Flint Beal 2007). The pathological hallmarks of the disease are the loss of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta and the presence of α-synuclein aggregates, named Lewy bodies (Thomas and Flint Beal 2007). The precise mechanisms underlying α-synuclein aggregation and nigral cell loss are unknown. Among others, oxidative stress, mitochondrial dysfunction, inflammation and dyshomeostasis of metals have been suggested to contribute to the pathogenesis of PD (Jomova et al. 2010).

The role of copper in PD is controversial, as some evidence points to a noxious role of copper in the pathology of PD, while other studies suggest a deficiency of copper in PD. Thus, copper has been demonstrated to bind to both soluble and membrane-bound α-synucleins with high affinity, to accelerate aggregation of

soluble α-synuclein (Uversky et al. 2001), and a copper-binding oligomer of α-synuclein has been discussed as neurotoxic form of α-synuclein (Brown 2010). However, while the total copper content in brains of PD patients does not differ strongly from healthy controls, copper levels are substantial lower in substantia nigra of PD patients (Loeffler et al. 1996; Ayton et al. 2013; Davies et al. 2014). This reduction in the copper content of the substantia nigra in PD has been discussed to result in the impairment of copper-dependent pathways, thereby contributing to the pathogenesis of PD (Double 2012; Ayton et al. 2013; Davies et al. 2014). In support of this view, copper supplementation (Alcaraz-Zubeldia et al. 2001, 2009) and the use of the BBB-permeable copper complex Cu(II)atsm (Hung et al. 2012) have been shown to be neuroprotective in animal models of PD, whereas copper chelation was not (Youdim et al. 2007).

Huntington's Disease

HD is a rare autosomal-dominant, progressive neurodegenerative disease characterized by motor, cognitive, and psychiatric abnormalities (Anderson 2011). HD is caused by polyglutamine expansion at the N-terminus of the huntingtin protein (McFarland and Cha 2011) that finally leads to brain atrophy, predominantly in the striatum and the cerebral cortex (Anderson 2011). Aggregation of the mutant huntingtin protein, oxidative stress, impaired energy metabolism, loss of neurotrophic support and transcriptional dysregulation have been discussed to contribute to development and progression of HD, but the exact pathogenic mechanism remains unknown. Accumulation of copper in the HD brain has been hypothesized to foster disease progression by promoting aggregation of the mutant huntingtin protein (Fox et al. 2007; Hands et al. 2010; Xiao et al. 2013). Further supporting a potential role of copper in disease progression, treatment with copper chelators, dietary copper reduction and genetic manipulation of copper transporters delayed disease progression in animal models for HD (Nguyen et al. 2005; Tallaksen-Greene et al. 2009; Cherny et al. 2012; Xiao et al. 2013).

Autism Spectrum Disorders

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders, including autistic disorder and Asperger syndrome, that are characterized by pervasive difficulties since early childhood across reciprocal social communication and restricted, repetitive interests and behaviors (Murphy et al. 2016). The etiology of ASD is currently unknown but is likely to be multifactorial encompassing both genetic and environmental factors (Murphy et al. 2016). There is some evidence for an alteration of copper homeostasis in ASDs. Homozygous deletions of the COMMD1 gene have been linked to autism (Levy et al. 2011), which loss of function results in copper overload in hepatic cell lines and is the cause of copper

toxicosis in Bedlington Terriers (Fedoseienko et al. 2014). Hair and nail samples of autistic children contain significant elevated levels of copper when compared to healthy controls and the levels of copper correlated positively with the severity of autism (Lakshmi Priya and Geetha 2011; Russo and de Vito 2011). Excess copper has further been shown to affect a pathway at the glutamatergic synapses associated with autism (Baecker et al. 2014).

Neurotoxicity of Copper Nanoparticles

Nanoparticles are usually defined as objects with at least two dimensions in the nanoscale (Borm et al. 2006). Due to their small size and their relative high surface, compared to the bulk material, they provide various interesting material properties. The chemical and physical properties of nanoparticles do not only depend on their size but also on their composition, shape, surface area, catalytic activity, and surface modifications (Kettler et al. 2014; Amin et al. 2015). Due to the huge variety of these materials, nanoparticles gained a lot of interest from industry and the scientific community over the last decades (Borm et al. 2006; Cupaioli et al. 2014).

The cheap price and the special features of copper oxide nanoparticles (CuO-NPs) led to an increased interest from the industry toward this material (Yurderi et al. 2015). However, despite their high application potential, there are various disadvantages of this material. The biocidal activity of CuO-NPs is a double-edged feature. On the one hand, CuO-NPs are effectively used in wood preservatives, anti-fouling paint, water filters, sterile surface coatings or textiles and bandages (Almeida et al. 2007; Ben-Sasson et al. 2014; Dankovich and Smith 2014). On the other hand, the biocidal activity of CuO-NPs could be unintentionally harmful to the human health and the environment (Karlsson et al. 2008).

It is important to elucidate the uptake and distribution of CuO-NPs in the body to understand the toxic mechanisms of CuO-NPs. Several studies report that nanoparticles are able to enter the body by different routes but inhalation is the most probable uptake route for nanoparticles, whereas the skin is hardly penetrated (Oberdörster et al. 2004; Borm et al. 2006; Kimura et al. 2012). Nanoparticles are able to enter the brain upon inhalation either directly by translocation over the nerve endings of the olfactory bulb or indirectly after uptake into the blood stream and crossing of the BBB (Kreyling et al. 2002; Oberdörster et al. 2004; Sharma and Sharma 2012). Especially for the occupational exposure scenario, it has to be considered that high amounts of Cu-containing NPs can unintentionally be released from electric motors or during welding (Szymczak et al. 2007). The majority of airborne copper is present as fine particles and nanoparticles. A recent study identified such airborne copper as source for poor motor neuron performance and altered basal ganglia in school kids, demonstrating the impact of nano-particular copper on the brain (Pujol et al. 2016).

The high toxic potential of CuO-NPs was demonstrated by in vitro studies on lung cell lines (Kim et al. 2013; Ivask et al. 2015). This high toxicity of CuO-NPs

was confirmed by in vivo inhalation and injection studies on rats and mice (Chen et al. 2006; Liao and Liu 2012; Privalova et al. 2014; Jing et al. 2015). Hereby, one particular inhalation study reported the high toxicity of CuO-NPs in comparison to the less toxic micrometer-sized copper oxide particles (Yokohira et al. 2008). In vivo studies have also shown that CuO-NPs can accumulate in the brain and have a high capacity to alter brain functionality (An et al. 2012; Privalova et al. 2014). The animals treated with CuO-NPs suffered severe cognitive impairments and damage of the BBB (An et al. 2012; Sharma and Sharma 2012). Wistar rats treated with CuO-NPs showed a decrease in learning and memory abilities as well as an impaired hippocampal LTP (An et al. 2012) which may involve the reported effects of CuO-NPs on neuronal potassium and sodium channels (Xu et al. 2009; Liu et al. 2011).

Several studies have evaluated the toxicity of CuO-NPs on brain cells including neurons (Li et al. 2007; Chen et al. 2008; Xu et al. 2009; Prabhu et al. 2010; Liu et al. 2011; Perreault et al. 2012) and astrocytes (Bulcke et al. 2014; Bulcke and Dringen 2014; Bulcke and Dringen 2016; Joshi et al. 2016). In contrast to iron oxide nanoparticles (Petters et al. 2014), CuO-NPs have a high toxic potential on primary cultured astrocytes (Bulcke and Dringen 2014) and alter in sub-toxic concentrations their glucose and glutathione metabolism and induce the synthesis of MTs (Bulcke and Dringen 2014; Bulcke and Dringen 2016). CuO-NP application leads to substantial cellular copper accumulation. CuO-NPs are likely to enter astrocytes by endocytotic mechanisms (Bulcke and Dringen 2016), but also extracellular liberation of copper ions has been suggested to be involved in the copper accumulation observed in glial cells after exposure to CuO-NPs (Joshi et al. 2016). The consequence of an exposure of cells to CuO-NPs is most likely mediated by an increase in cytosolic copper concentration which is caused by accumulation of copper liberated from particles rather than adverse particle effects (Bulcke and Dringen 2016). Thus, the reported toxicity of CuO-NPs to brain cells is most likely mediated by accelerated ROS production and oxidative damage (Bulcke et al. 2014).

Conclusions

Copper is an essential trace element which is involved in a large variety of different cellular functions. However, as copper in excess leads to accelerated formation of ROS and inactivation of cellular enzymes, the availability of copper is tightly regulated both on the systemic and cellular level. Both excess of copper and copper deprivation have severe adverse consequences on cells and organism as clearly shown by the different types of neurodegenerative disorders which have been connected with disturbances in copper homeostasis. The dilemma that sufficient amounts of copper have to be available but that an excess of copper has to be prevented makes therapeutic approaches to correct disturbances of copper homeostasis in neurological disorders a challenging task.

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