Chapter 28
The Importance of Trace Elements for Neurological Function

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Keywords Iron • Manganese • Copper • Zinc • Nutritional Deficiency • Neurotransmitters • Neurodegeneration

Abbreviations

Aβ	Amyloid beta protein
AD	Alzheimer's disease
APP	Amyloid precursor protein
BBB	Blood-brain barrier
BCB	Blood cerebral spinal fluid barrier
CNS	Central nervous system
CSF	Cerebrospinal fluid
Ctr-1	Copper transporter-1
DAT	Dopamine transporter
DMT-1	Divalent metal transporter-1
GABA	Gamma-aminobutyric acid
GAT	GABA transporter
ID	Iron deficiency
IRE	Iron response element
IRP	Iron regulatory protein
MNK	Menkes copper ATPase
MRI	Magnetic resonance imaging
NET	Norepinephrine transporter
NMDA	*N*-methyl-d-aspartate
PD	Parkinson's disease
SOD	Superoxide dismutase
TfR	Transferrin receptor
UTR	Untranslated region
WND	Wilson's copper ATPase
ZnT	Zinc transporter

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28.1 Introduction

The essentiality of micronutrients for proper development and function of biological systems has long been recognized. By participating in oxidation-reduction reactions, trace elements play a role in various cellular metabolic processes. However, the dual nature of dietary metals requires that they must be both available to cells and stringently regulated. Disturbances in the homeostasis of these metals can have deleterious effects, specifically in the central nervous system (CNS), resulting in substantial injury to neurons and glia through oxidative damage, in turn leading to neurodegeneration and neurological dysfunction (see Table 28.1). This chapter will focus on iron, manganese, copper, and zinc, essential metals required for numerous important processes in mammalian systems, particularly the CNS (Aschner et al. 2005; Burhans et al. 2005; Arredondo and Núñez 2005; Donnelly et al. 2007).

Iron plays a crucial role as a component of various enzymes and is required for oxidative phosphorylation, nitric oxide metabolism, and oxygen transport (Donnelly et al. 2007). Found throughout the brain, with the highest concentrations in the basal ganglia and the white matter, iron is involved in the synthesis of neurotransmitters and myelin, playing an essential role in neuronal function (Table 28.2) and as a cofactor for a variety of metalloenzymes (Table 28.3) (Beard et al. 1993). As a critical component in dozens of proteins and enzymes, manganese is present in all mammalian tissues and is active in maintaining normal immune function, regulation of blood sugar, and cellular energy, reproduction, digestion, bone growth, defense against free radicals, and blood clotting in concert with vitamin K (Aschner et al. 2005).

Copper is an essential component for a variety of critical enzymes in metabolism, as outlined in Table 28.3. Required for cellular respiration, iron oxidation, and pigment formation, copper also plays a role in neurotransmitter biosynthesis, antioxidant defense, peptide amidation, and connective tissue formation (Madsen and Gitlin 2007). Almost 100 enzymes in mammalian systems require zinc as a cofactor (Table 28.2) (NAS 2002). Zinc is highly abundant in mammalian tissue second only to iron (McCall et al. 2000), and present predominately in the brain (Szewczyk et al. 2008). A major regulator of synaptic transmission and other neuronal processes, zinc is present in the synapse at millimolar concentrations (Donnelly et al. 2007).

28.2 Uptake and Transport of Metals in the Brain

28.2.1 Iron

Iron is widely distributed throughout the various cell types of the CNS, but is particularly abundant in astrocytes, lending credence to the hypothesis that glial cells function in iron storage and regulation (Madsen and Gitlin 2007). The highest concentrations of iron within the brain occur in the basal

Table 28.1 Key facts about trace elements that are important for normal brain functioning

1. The primary essential trace elements that are important for normal brain functioning are iron, manganese, copper, and zinc
2. These trace elements are critical for normal motor control, appetite regulation, learning, memory, mood, and several other neurological functions
3. Brain cells have multiple mechanisms for ensuring adequate trace element availability
4. A lack of these trace elements will cause devastating neurological problems ranging from behavioral to cognitive deficiencies
5. An overload of these trace elements is linked with neurodegenerative diseases (e.g., Parkinson's disease and Alzheimer's disease)

This table lists the key facts about neurologically relevant essential trace elements

Table 28.2 Key brain functions of selected trace elements

Metal	Function
Iron	• Cofactor essential for synthesis of ATP in the brain • Maintains sufficient oxygen levels in the brain as a component of hemoglobin • Functions as a cofactor in the enzymes responsible for the synthesis of biogenic amine neurotransmitters • Critical role in myelinogenesis • Important for packaging, uptake, and degradation of neurotransmitters
Manganese	• Cofactor essential for production of ATP via gluconeogenesis • Antioxidant functions through the action of Mn-SOD • Regulates brain ammonia levels as a component of glutamine synthetase
Copper	• Antioxidant function through the action of Cu/Zn-SOD • Ferroxidase activity as a component of ceruloplasmin and hephaestin • Critical for production of norepinephrine through the action of dopamine β-hydroxylase • Participates in oxidative phosphorylation as a cofactor of cytochrome *c* oxidase • Plays role in brain development through synaptogenesis
Zinc	• Trace element with the highest intracellular abundance • Involved in protein synthesis • Cofactor in a myriad of enzymes involved in all aspects of metabolism • Regulates synaptic activity and neuronal processes • Critical role in regulation of gene transcription • Important for synaptogenesis and neuronal growth

This table lists the key brain functions attributed to enzymes or processes that depend on the listed trace element. Many functions are related to neurotransmitter biology and chemistry

Table 28.3 Selected metalloenzymes

Metal	Enzyme	Function	Consequences of loss
Iron	Tyrosine hydroxylase	Dopamine synthesis	Dystonia and movement disorders
	Tryptophan hydroxylase	Serotonin synthesis	Anxiety and pulmonary dysfunction
	Xanthine oxidase	Catabolism of purines	Hematuria
	Ribonucleotide reductase	Rate limiting step in DNA synthesis	Embryonic lethality
	Cytochrome P450s	Various metabolic pathways	Altered metabolism, congenital defects, and embryonic lethality
	Catalase	Antioxidant defense	Oxidative damage
Manganese	Glutamine synthetase	Regulation of ammonia levels	Severe brain malformations
	Phosphoenolpyruvate carboxykinase	Gluconeogenesis	Altered ATP synthesis
	Manganese superoxide dismutase	Antioxidant defense	Oxidative damage
Copper	Lysyl oxidase	Crosslink formation in collagen and elastin	Perinatal death
	Peptidylglycine α-amidating monooxygenase	Activation of peptides with α terminal glycine	Embryonic lethality
	Copper/zinc superoxide dismutase	Antioxidant defense	Oxidative damage
	Ceruloplasmin	Ferroxidase	Iron overload, anemia, diabetes, and neurodegeneration
	Hephaestin	Ferroxidase	Impaired iron absorption, anemia
	Dopamine β-hydroxylase	Norepinephrine synthesis	Impaired sympathetic regulation
	Cytochrome *c* oxidase	Oxidative phosphorylation	Encephalopathy
Zinc	Copper/zinc superoxide dismutase	Antioxidant defense	Oxidative damage
	Alcohol dehydrogenase	Catabolism of alcohol	Decreased retinol utilization
	Carbonic anhydrase	Conversion of carbon dioxide to carbonate	Osteopetrosis

This table highlights key enzymes that are dependent upon the divalent metals for proper functioning. The role of the enzyme as well as the pathologies associated with its dysfunction are listed by column

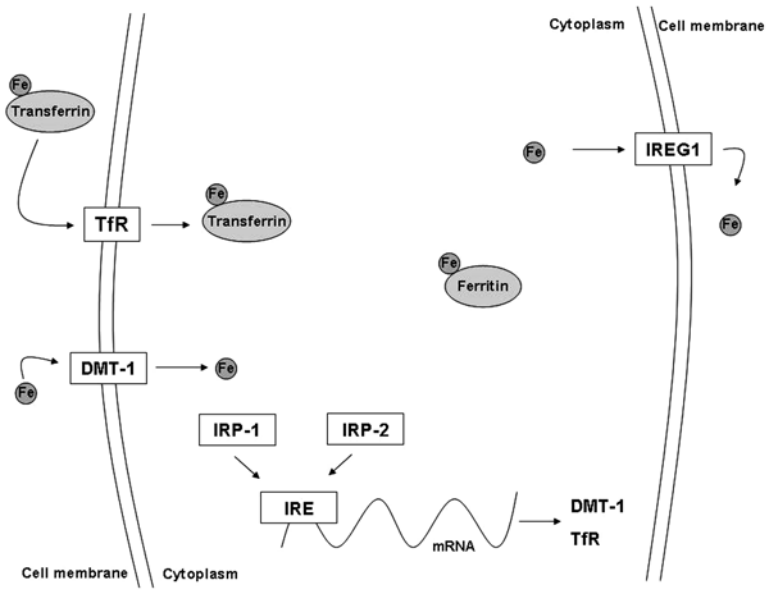

Fig. 28.1 Basic cellular iron transport. Mechanisms of cellular iron transport within the brain are illustrated, including known transport proteins and pathways. Iron may enter cells via transferrin-mediated transport or via the divalent metal transporter (*DMT-1*). Once inside the cell, iron is stored complexed with ferritin. Iron may be excreted from cells by ferroportin, also known as IREG-1. Iron regulatory proteins such as IRP-1 and IRP-2 bind iron responsive elements (*IRE*) in response to changes in iron homeostasis, influences the transcription of iron transport proteins, such as TfR and DMT-1

ganglia at levels equivalent to those observed in the liver, suggesting that the basal ganglia may act as a region of iron storage and distribution within the brain (for a more thorough review, see Beard et al. 1993). Transferrin, a plasma glycoprotein transporting iron in the periphery, is responsible for the shuttling of iron across the blood-brain barrier (BBB) (Madsen and Gitlin 2007) (Fig. 28.1). The highest levels of transferrin in the brain occur in regions containing more myelin, and in the white matter more so than the gray matter. The synthesis of myelin from fatty acids and cholesterol by oligodendroglia is an iron-dependent process (Beard et al. 1993).

One-third of brain iron is stored as ferritin, which is ten-fold more abundant in the brain than transferrin, mostly in oligodendroglia and microglia. Ferritin is comprised of either a heavy chain, which takes up and releases iron more rapidly and is found predominately in neurons, or a light chain, found mostly in glia (Beard et al. 1993). This implies that within the brain, cell populations regulate iron levels in differing ways. The mature brain gains iron through BBB and the brain-cerebral spinal fluid barrier (BCB) via pathways dependent upon transport by transferrin receptor (TfR) and divalent metal transporter-1 (DMT-1), a transporter of divalent metals present in astrocytes (Siddappa et al. 2003). Expression of both TfR and DMT-1 is regulated by the iron regulatory proteins IRP-1 and IRP-2, cytosolic proteins sensitive to decreases in intracellular iron status. These proteins bind to an iron response element (IRE) on 3′ UTR of TfR and DMT-1 mRNA when intracellular iron is low, increasing the stability of the mRNA and increasing protein expression (Fig. 28.1). The brain has two mechanisms to increase iron delivery to neurons: increasing total brain iron delivery from serum via BBB and BCB and/or increasing the percentage of cells expressing TfR and DMT-1 (Siddappa et al. 2003).

28.2.2 Manganese

Most brain manganese is found in the iron-rich regions of the basal ganglia. Transport of manganese into the CNS may occur via the blood at the BBB or via cerebral spinal fluid at the BCB (Aschner et al. 2005), with the entry of manganese into the CNS via the BCB increasing with elevated plasma concentrations of manganese (Normandin et al. 2004). Manganese may also enter the brain following inhalation, bypassing the normal systemic regulatory processes and delivering manganese directly to the CNS. This may occur via the olfactory nerve, the epithelia, or a more systemic route through the mucosa (see Erikson et al. 2007 for review of brain manganese transport). In the brain, manganese can migrate to most regions utilizing a variety of mechanisms. Axonal transport of manganese has been demonstrated, as well as the ability of manganese to cross synapses and travel along secondary and tertiary neurons (Aschner et al. 2005). Manganese may also enter neurons and glial cells through calcium channels (Aschner et al. 2005). To date, the precise mechanism of manganese transport in the brain is still unknown and probably consists of more than one primary route. Facilitated diffusion, active transport, and transferrin-dependent transport are all proposed mechanisms of manganese transport across the BBB (Aschner et al. 2005) (Fig. 28.2). A recent study demonstrated that inhibition of DAT inhibits manganese accumulation in the globus pallidus during chronic exposure, suggesting that the DAT may not play a central role in normal manganese transport in the brain, but may become relevant in a toxicological paradigm in terms of manganese exposure (Anderson et al. 2007). Other transporters recently implicated in the manganese transport include the monocarboxylic acid transporter and the organic anion transporter (Crossgrove et al. 2003), as well as the Zrt/Irt-like proteins (ZIP) (He et al. 2006) (Fig. 28.2).

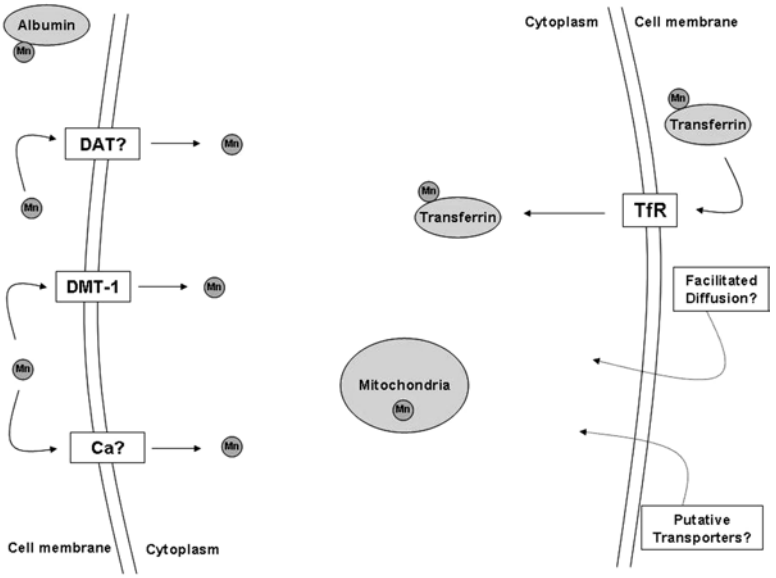

Fig. 28.2 Basic cellular manganese transport. Mechanisms of cellular manganese transport within the brain are illustrated, including known and hypothesized transport proteins and pathways. Manganese may enter cells via transferrin-mediated transport or via the divalent metal transporter DMT-1, though the exact mechanism of manganese absorption is not completely understood and may include facilitated diffusion or other putative transporters, such as the monocarboxylic acid transporter, organic anion transporter, or ZIP transporter. DAT and calcium channels have been shown to allow entry of manganese into the cell. Inside the cell, the mitochondria act as a sink for manganese

28.2.3 Copper

Copper is distributed across most regions of the brain, with the highest levels found in the basal ganglia (Madsen and Gitlin 2007). Transport of copper is dependent upon the oxidation state, with the reduced form of copper being the only form able to be transported (Macreadie 2008). Additionally, metallochaperone proteins, such as Atox1, bind and transport copper to specific locations within the cell in a pathway-specific manner (Fig. 28.3). Since excess and free copper is toxic to cells, sequestration is essential through copper-binding proteins such as metallothionein, a cysteine-rich cytoplasmic protein that chelates copper and is essential to protect against toxicity (Madsen and Gitlin 2007). Two transporting ATPases, Atp7a (MNK) and Atp7b (WND), are the main proteins regulating cellular copper homeostasis (Arredondo and Núñez 2005). MNK excretes copper from most cells when concentrations become too high, while WND performs this function in hepatocytes, excreting copper into the bile. Both transport proteins supply copper for enzymes by shuttling copper into the Golgi (Fig. 28.3). Additionally, in the brain MNK is expressed within specific populations of neurons in several brain regions, including the cerebellum and hippocampus, as well as the BBB endothelium, and facilitates copper movement (Madsen and Gitlin 2007). Copper transporter-1 (Ctr-1) is a plasma membrane protein present on the endothelium of the BBB and essential for early embryonic development (Madsen and Gitlin 2007). Expression of Ctr-1 increases during perinatal copper deficiency (Arredondo and Núñez 2005), suggesting that Ctr-1 transports copper into the brain from the plasma. DMT-1 (Arredondo and Núñez 2005) and amyloid precursor protein (APP) (Macreadie 2008) are also likely copper transporters in the brain (Fig. 28.3).

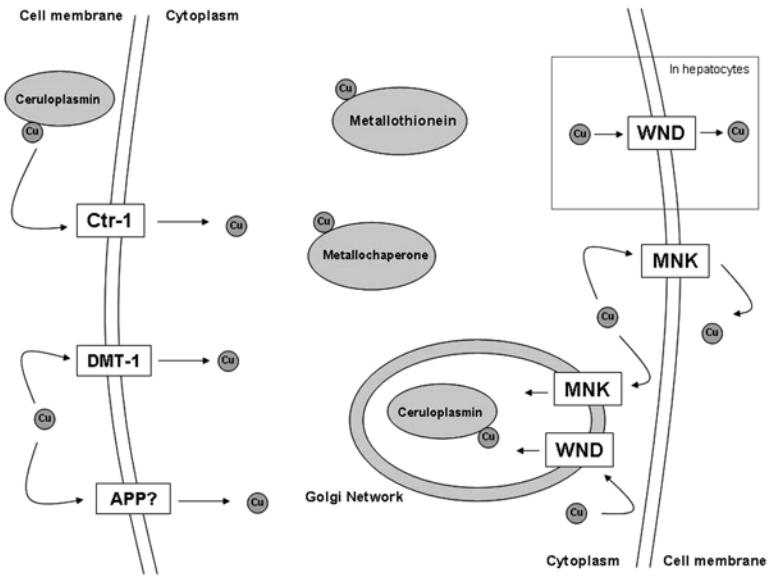

Fig. 28.3 Basic cellular copper transport. Mechanisms of cellular copper transport within the brain are illustrated, including known and hypothesized transport proteins and pathways. Copper may enter the cell through the copper transporter Ctr-1 or DMT-1. The amyloid precursor protein may act as a copper transport protein as well. Inside the cell, copper is bound to metalloproteins such as ceruloplasmin or metallothionein to prevent cytotoxicity of free copper. Metallochaperone proteins direct copper in a pathway-specific manner to organelles for incorporation of copper into metalloenzymes. MNK and WND transport copper into the Golgi network for processing and packaging. MNK can also transport copper out of the cell, with this function being performed by WND in hepatocytes

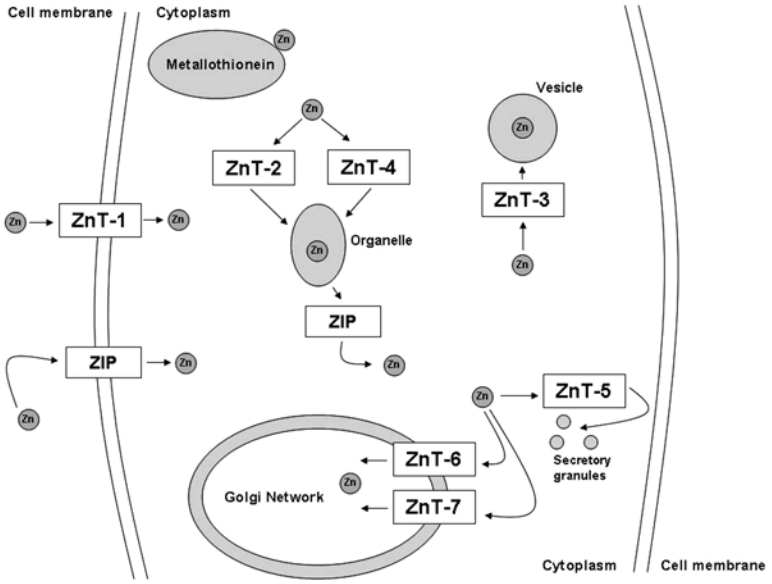

Fig. 28.4 Basic cellular zinc transport. Mechanisms of cellular zinc transport within the brain are illustrated, including known and hypothesized transport proteins and pathways. Zinc may enter the cell via zinc transporter 1 (*ZnT-1*) or through Zn/Irt proteins (*ZIP*). Inside the cell, zinc may be transported via ZnT-2 or ZnT-4 into organelles, ZnT-3 into vesicles, ZnT-5 into secretory granules, or ZnT-6 or ZnT-7 into the Golgi network. Free zinc in the cell is usually bound to a metalloprotein such as metallothionein to prevent toxicity

28.2.4 Zinc

The presence of zinc within the brain, particularly the cerebellum, has been known for the past several decades (Reviewed in: Sandstead et al. 2000). Brain zinc concentrations are highest in the telencephalon, hippocampus, amygdala, and gray matter of the cortex. The vast majority of zinc in the brain is bound to metalloproteins, such as metallothionein, with the rest found in presynaptic vesicles (Szewczyk et al. 2008). Zinc is found highly concentrated within neurons of the CNS (Sandstead et al. 2000). Several zinc transporters (ZnT) have been identified and are crucial for the movement of zinc within mammalian systems (Fig. 28.4). ZnT-1 lowers intracellular zinc, preventing toxicity, since moderate increases in the concentration of intracellular zinc can lead to cytotoxicity. ZnT-2 and ZnT-4 sequester zinc into organelles, with ZnT-6 and ZnT-7 moving zinc into the Golgi and ZnT-5 transporting zinc into secretory granules. ZnT-3 and ZnT-4 are found in the CNS, with ZnT-3 responsible for transporting zinc into vesicles (Sandstead et al. 2000). Zrt/Irt-like proteins (ZIP) transport zinc into the cytoplasm from both the extracellular space and from zinc-containing organelles (Nakashima and Dyck 2009) (Fig. 28.4).

28.3 Role of Metals in Brain Development

28.3.1 Iron

Iron is extremely important to the developing nervous system, with the rate of iron uptake by the brain greatest during fetal life (for review see Madsen and Gitlin 2007), coinciding with a peak in myelinogenesis, with perinatal ID significantly altering myelination of the spinal column and the

white matter of the cerebellum. Iron requirements in the brain far exceed brain iron uptake, suggesting that most of the iron in the brain used daily is recycled behind the BBB, with recycling a major source of iron for brain function following birth. This is analogous to what occurs with regard to iron homeostasis in the periphery (Madsen and Gitlin 2007).

28.3.2 Manganese

Manganese is essential for the functioning and development of the brain and manganese distribution within the brain varies across the life cycle, with concentrations higher in adults than in infants. Alterations in brain Mn levels might be associated with brain maturation and function (Takeda 2003). Manganese is highly concentrated in the hippocampus and pons following birth, structures that may require high levels of manganese, and is found in high concentrations within regions of the basal ganglia in the adult brain, with movement of manganese within the brain likely associated with neuronal activity.

28.3.3 Copper

Copper is essential for CNS development, with studies suggesting a role for MNK and copper in axon extension and synaptogenesis during brain development (Madsen and Gitlin 2007). Disruption of copper homeostasis during fetal life can lead to perinatal mortality, severe growth retardation, and neurodegeneration. Timing of perinatal copper deficiency influences the severity of the neurological outcomes, suggesting a critical period for adequate copper in brain development (Madsen and Gitlin 2007). Rapid growth increases copper demands, with infancy representing the most critical period for copper requirements (Arredondo and Núñez 2005). Diets based on milk provide low amounts of copper and deficiency is of greatest concern during this stage. Also at this stage there is an increased risk of toxic effects due to immature liver functioning unable to handle high copper exposure (Arredondo and Núñez 2005).

28.3.4 Zinc

Zinc plays a role in synaptogenesis and neuronal growth during early brain development, with deficiency during these stages causing malformations and behavioral alterations. Zinc is required for DNA and protein synthesis in the embryo, as well as dendritic growth and motor development. Deficiency of zinc during embryonic development can lead to stunted fetal growth, though concentrations of zinc are higher in adults than in newborns (Sandstead et al. 2000).

28.4 Effects of Metals on Neurotransmitter Systems

28.4.1 Iron

The role of intraneuronal iron includes incorporation of iron into enzymes for oxidation-reduction reactions, electron transport, and synthesis, packaging, uptake, and degradation of neurotransmitters (Beard et al. 1993) (Fig. 28.5). Iron is involved in the synthesis of catecholamines, with iron status

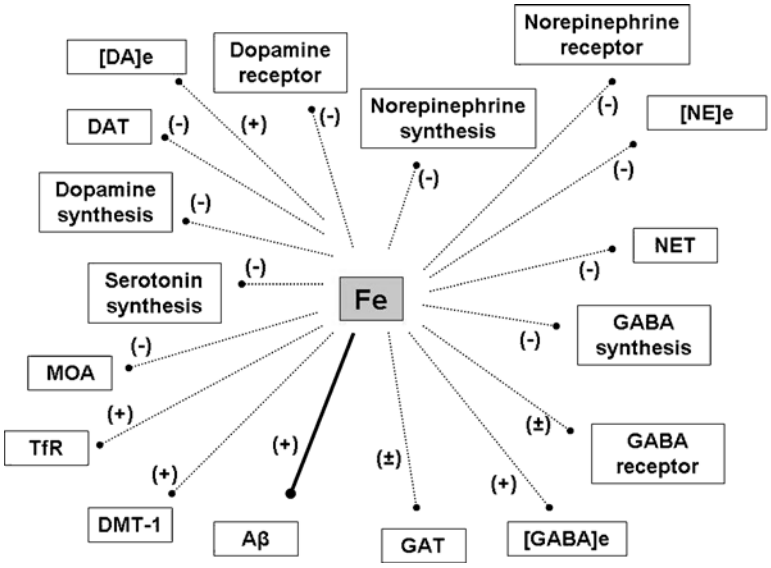

Fig. 28.5 Role of iron in neurotransmitter biology. Increases (+) and decreases (–) in activity resulting from the effects of iron on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)

hypothesized to affect both monoamine oxidase and aldehyde dehydrogenase, enzymes critical for the catabolism of these biogenic amines. Alterations in iron homeostasis can negatively impact synthesis of γ-aminobutyric acid (GABA) (Beard et al. 1993), as well as expression of GABA transport and receptor proteins (Anderson et al. 2008). Over two decades ago, ID was linked to alterations in dopamine receptor expression (Youdim et al. 1989), with more recent studies observing increased extracellular dopamine and decreased functioning of dopamine receptors (Beard et al. 2006). Studies have found effects of ID on norepinephrine pool size, norepinephrine uptake, and norepinephrine transporter expression both in vitro and in vivo (Beard et al. 2006).

28.4.2 Manganese

Manganese has been shown to block voltage-dependent Ca channels and nerve-evoked neurotransmitter release (Takeda 2003) (Fig. 28.6). Manganese may be released concurrently with glutamate and can decrease the ability of astrocytes to clear glutamate from the synapse, which is likely linked to downregulation of the glutamate:aspartate transporter (Fitsanakis and Aschner 2005). Additionally, manganese has been shown to increase both the frequency and amplitude of spontaneous excitatory post-synaptic potentials in the striatum, leading to increased extracellular glutamate (Fitsanakis and Aschner 2005). Manganese is known to affect GABA by dose-dependently increasing binding at $GABA_B$ receptors (Kerr and Ong 1995), with manganese exposure leading to perturbations in expression of GABA transport and receptor proteins (Anderson et al. 2008). Manganese exposure has also been shown to decrease density of the dopamine transporter (DAT) in rodent models (McDougall et al. 2008). Data from nonhuman primate studies point to a reduction in dopamine receptors postsynaptically in response to manganese exposure (Eriksson et al. 1992). Loss of autoreceptor control of dopamine activity during early stages of manganese poisoning has been demonstrated in mice as

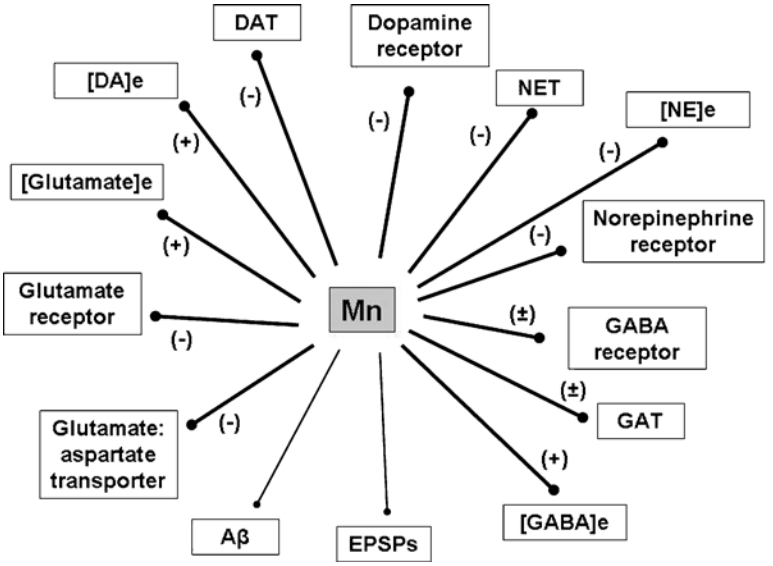

Fig. 28.6 Role of manganese in neurotransmitter biology. Increases (+) and decreases (–) in activity resulting from the effects of manganese on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)

well (Cuesta de Di Zio et al. 1995), affecting extracellular levels of dopamine and expression of DAT. Struve et al. (2007) found marginal increases in GABA and norepinephrine in response to manganese exposure in primates. A study by Autissier et al. (1982) found alterations in tissue concentrations of norepinephrine in a rodent model, while manganese was found to inhibit uptake of norepinephrine in a dose-dependent manner ex vivo (Lai et al. 1982). Additionally, manganese exposure has been shown to decrease cellular concentrations of serotonin (Reaney and Smith 2005).

28.4.3 Copper

At some neurons, copper may be co-released at the synapse with classical neurotransmitters (Madsen and Gitlin 2007). Copper plays a role in long-term potentiation, modulating activity of calcium-dependent cascades, and synaptic plasticity (Fig. 28.7). Copper is an antagonist at NMDA receptors, leading to rapid and reversible trafficking by MNK, suggesting a mechanism linking copper homeostasis and neuronal activation. The neurotransmitter norepinephrine is a catecholaminergic neuromodulatory neurotransmitter derived from dopamine by dopamine β-hydroxylase, a copper-dependent enzyme (Madsen and Gitlin 2007).

28.4.4 Zinc

Zinc may be co-released at the synapse with classical neurotransmitters and can modulate GABA, NMDA, and glycine receptors at micromolar concentrations (Fig. 28.8). A special class of glutamatergic neurons has zinc-containing vesicles in the axon terminals, releasing zinc into the synaptic cleft and modulating post-synaptic NMDA receptors (Sandstead et al. 2000). All zinc-containing neurons are glutamatergic, but not vice versa (Donnelly et al. 2007), with zinc-containing somata located almost

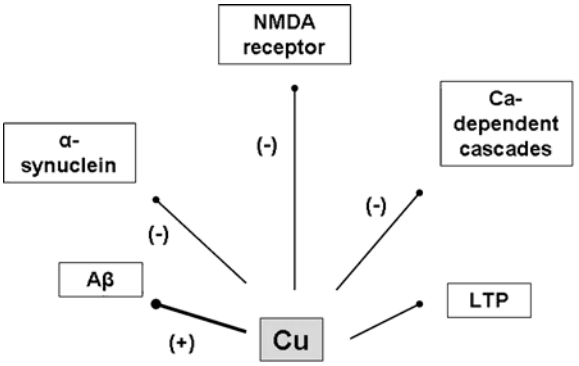

Fig. 28.7 Role of copper in neurotransmitter biology. Increases (+) and decreases (−) in activity resulting from the effects of copper on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)

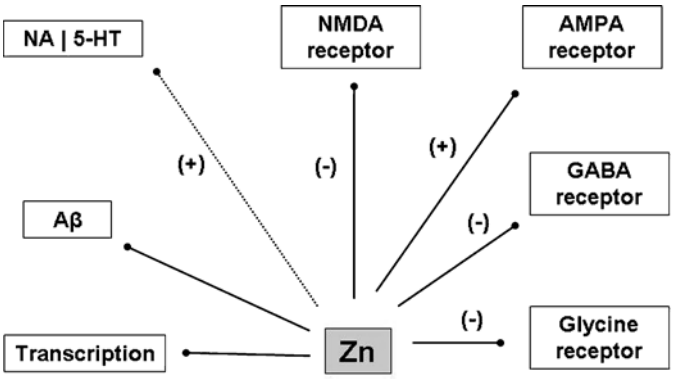

Fig. 28.8 Role of zinc in neurotransmitter biology. Increases (+) and decreases (−) in activity resulting from the effects of zinc on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)

exclusively in cerebral cortex and amygdala. Zinc alters neuronal excitability, plays a role in synaptic plasticity, and can function as a signaling molecule affecting protein function (Szewczyk et al. 2008). Zinc is an inhibitor of GABA receptors, binding to the extracellular domain and allosterically stabilizing the receptor into a shut formation without blocking the channel (Gingrich and Burkat 1998). Zinc also inhibits the GABA transporter (Nakashima and Dyck 2009). Zinc-ATP is necessary for the synthesis of pyridoxal-5-phosphate and flavin adenosine dinucleotide, coenzymes that are essential for the synthesis of biogenic amines and monoamine oxidase metabolism. Severe zinc deficiency has been shown to increase brain concentrations of norepinephrine in rodent models (Sandstead et al. 2000).

28.5 Effects of Altered Metal Homeostasis

28.5.1 Deficiency

28.5.1.1 Iron

Iron deficiency is reported as the most prevalent nutritional problem in the world, affecting more than two billion individuals worldwide (WHO/UNICEF/UNU 2006), and is associated with malformation of red blood cells, growth impairment, perturbations in thermoregulation, and deficits in cognitive function (Beard et al. 1993). The neurobiological sequelae of ID in humans include variations in behavior, cognition, and neurotransmitter metabolism, including anemia, reduced immune function, diminished work capacity, and impaired thermoregulation. Disturbances in iron homeostasis

are linked to cognitive dysfunction, neurodegenerative diseases, restless leg syndrome, and Parkinson's disease (Burhans et al. 2005). Iron deficiency in early life may lead to insufficient myelination and dysfunction of dopaminergic tracts (Arredondo and Núñez 2005), as well as neuropsychological effects linked to delayed cognitive development in children and adolescents, delays that may respond to iron therapy (Sandstead et al. 2000). Iron deficiency during late fetal and early postnatal life is associated with cognitive impairments that persist despite repletion, presumably due to alterations in iron-based neuronal cellular processes that occur during the period of rapid brain growth and high iron demand (Siddappa et al. 2003). During the perinatal period, ID results in regionalization of functional brain iron, which may depend on the responsiveness of TfR and DMT-1 and the regulatory proteins IRP-1 and IRP-2 (Siddappa et al. 2003). Studies that have followed children several months after iron repletion suggest that there is an early critical period of brain development during which ID can have a permanent impact (for review, see Youdim 2001).

28.5.1.2 Manganese

Because of its widespread presence in human diets, frank manganese deficiency is generally not clinically recognized in humans. Manganese deficiency has been observed in laboratory animals and has been associated with impaired growth, skeletal defects, reduced reproductive function, birth defects, and abnormal glucose tolerance, as well as altered lipid and carbohydrate metabolism (Aschner et al. 2005). Reduced manganese status may also be observed in individuals with osteoporosis and epilepsy. Blood manganese concentrations are lower in epileptic patients, and alterations in brain manganese homeostasis may be associated with susceptibility to seizures. People with exocrine pancreatic insufficiency, chronic hemodialysis, Perthes' disease, and phenylketonuria may also possess inadequate manganese levels (Aschner et al. 2005).

28.5.1.3 Copper

Frank copper deficiency is rare in humans, though it has been observed in infants fed milk formulas and those recovering from malnutrition, or in adult patients receiving prolonged total parenteral nutrition (Fujita et al. 1989). Symptoms of copper deficiency include anemia, leukopenia, neutropenia, and osteoporosis (Fujita et al. 1989). During severe copper deficiency, iron transport within the body is adversely affected (Arredondo and Núñez 2005), with iron tending to accumulate in many tissues, followed by anemia. Acquired copper deficiency in adults leads to myelopathy, limb spasticity, and sensory ataxia due to neurodegeneration (Madsen and Gitlin 2007).

28.5.1.4 Zinc

Zinc deficiency is not uncommon and may present simultaneously with ID. Both metals are most bioavailable from similar food sources and absorption of both is inhibited by the same dietary substances (Sandstead and Smith 1996). Zinc deficiency causes abnormal development of the nervous system, leading to distinct behavioral effects (Sandstead et al. 2000). Depression and impaired cognitive function are early clinical manifestations of zinc deficiency, with lower serum zinc levels found in depressed individuals, which may be normalized after successful antidepressant therapy (Szewczyk et al. 2008). Zinc deficiency has been reported in Alzheimer's disease (AD) patients and could be a contributing factor in development of this condition (Shcherbatykh and Carpenter 2007).

28.5.2 Overload/Toxicity

28.5.2.1 Iron

Dysregulation of iron homeostasis in the brain leading to increased concentrations of iron result in saturation of iron transport and storage proteins, increased free iron in the cell, production of reactive oxygen species, oxidative damage, and cell death via apoptosis (Beard et al. 1993). Accumulation of iron in the brain occurs with aging, along with an increase in ferritin. This increase may lead to oxidative damage as a result of proxidant-free iron, which may be released from ferritin under acidic condition caused by excess concentrations of SOD or ascorbate, intracerebral hemorrhage, or hypoxic ischemia (Gaasch et al. 2007). High concentrations of brain and dysregulation of iron homeostasis in the brain are associated with Parkinson's disease (PD) and Alzheimer's disease (AD), which will be described further in the Applications to Health and Disease section of this chapter. Interestingly, inherited disorders of iron metabolism such as hemochromatosis do not always correlate with increased brain iron (Gaasch et al. 2007).

28.5.2.2 Manganese

Manganese toxicity resulting from environmental exposure has been documented since the early nineteenth century, when a small group of workers grinding manganese oxide developed an unsteady gait and muscular weakness (Normandin et al. 2004). At present, manganese toxicity is most often associated with occupational exposure of welders, miners, and steel workers to chronic high levels of airborne particulate manganese (Pal et al. 1999). When inhaled, the manganese can lead to inflammation in the lungs and potential respiratory symptoms, including cough, bronchitis, pneumonitis, and impaired pulmonary function (Roels et al. 1987). Cases from drinking contaminated well water have also been reported in several countries, resulting in impaired cognitive function (Sahni et al. 2007). Working memory, concentration, and spatial orientation have all been shown to be affected following toxic manganese exposure (Mergler et al. 1994). Manganese neurotoxicity is characterized by a psychiatric disorder resembling schizophrenia, and eventually manifests as a neurological disorder sharing similarities with several clinical disorders, in particular Parkinson's disease (Pal et al. 1999).

28.5.2.3 Copper

At steady state the amount of copper excreted into the bile is equivalent to that absorbed from the intestine, with excretion increasing promptly in response to elevated dietary copper. Therefore, excess copper does not occur in the absence of an underlying metabolic defect (Madsen and Gitlin 2007). The consequences of these genetic disorders of copper metabolism are discussed in the section, Applications to Health and Disease.

28.5.2.4 Zinc

High intracellular concentrations of zinc are cytotoxic and can lead to neurodegeneration through the production of ROS, resulting in oxidative damage. It is hypothesized that excess zinc leads to cell death by inhibiting synthesis of ATP at various points in cell metabolism. Zinc has been shown to

disrupt glycolysis, the Kreb's cycle, and the electron transport chain through the inhibition of specific enzymes required for these processes. These high levels of intracellular zinc may be achieved through the influx of zinc from the extracellular space through ion channels of glutamate receptors. Moreover, zinc has been implicated as a potential neurotoxin in models of stroke and epilepsy, and high levels of zinc can lead to aggregation of amyloid plaques and dementia in neurodegenerative diseases (Dineley et al. 2003).

28.6 Applications to Health and Disease

Imbalance of trace metals can play a role in the etiology of various neurodegenerative and neurological disease states. Cellular levels of Fe and transferrin are altered around plaques present in multiple sclerosis, with iron contained in sclerotic plaques and MRI data from multiple sclerosis patients showing a general disruption in regulation of iron (Beard et al. 1993). Human prions have been shown to have binding sites for trace metals (Shcherbatykh and Carpenter 2007). Moreover, individuals suffering from a complete deficiency of ceruloplasmin have alterations in iron metabolism and develop dementia later in life (Madsen and Gitlin 2007). Altered brain metal homeostasis has been implicated in Huntington's disease, Freidreich's ataxia, and amyotrophic lateral sclerosis (Aschner et al. 2005; Gaasch et al. 2007). Parkinson's disease (PD) and Alzheimer's disease (AD) are two neurodegenerative conditions in which altered homeostasis of metals is of keen interest. Additionally, genetic disorders of copper metabolism deleteriously impact neurological function.

28.6.1 Parkinson's Disease

Parkinson's disease is one of the most common neurodegenerative conditions among the elderly, affecting a marginal percentage of the worldwide population (Rommelfanger and Weinshenker 2007). Disturbed iron homeostasis has been linked to cognitive dysfunction and PD (Burhans et al. 2005), with the postmortem brain iron content of PD patients significantly higher than that of age-matched controls (Beard et al. 1993). Manganese neurotoxicity shares similarities with PD (Pal et al. 1999), and manganese accumulation in the brain may play a role in the pathology of idiopathic PD (for review, see Aschner et al. 2005). Copper affects oligomerization of α-synuclein, a protein essential for neurotransmission, during PD (Macreadie 2008). Additionally, alterations in norepinephrine biology brought on by perturbations in metal homeostasis may play a role in the etiology of PD given the profound effects of norepinephrine on brain inflammation, oxidative stress, and the function of protein implicated in the condition (Rommelfanger and Weinshenker 2007).

28.6.2 Alzheimer's Disease

Recently, there has been substantial interest in role of copper, zinc, manganese, and iron in the neuropathology of AD, since these metals are known to be concentrated in and around amyloid plaques at concentrations three to five times higher than in age-matched controls (Shcherbatykh and Carpenter 2007).

Additionally, there is an observed imbalance of these metals (decreased copper; increased iron, manganese, and zinc) in the AD brain, with chelators having been shown to enhance resolubilization of plaques (Cornett et al. 1998). However, the exact role of these trace metals in AD pathogenesis remains uncertain (Shcherbatykh and Carpenter 2007).

Iron is a component of senile plaques and iron encrustation of blood vessels is common in AD. Iron mobility decreases and iron levels in the brain are increased during AD, with an associated decrease in metabolic activity and increase in perioxidative damage. IRE is located on the mRNA for the amyloid precursor protein (Beard et al. 1993). Compared to normal aged tissue, the concentration of transferrin decreases, ferritin levels decrease, and iron levels increase in tissues from AD patients, with loss of the transferrin receptor observed the in AD brains (Beard et al. 1993). The amyloid β protein (Aβ), which forms the senile plaques in AD, reduces copper and iron leading to production of hydrogen peroxide and toxicity (Shcherbatykh and Carpenter 2007). Copper can induce Aβ precipitation, with Aβ having selective binding sites for copper, making the copper in Aβ plaques available for reactive oxygen species production (Macreadie 2008). A clear association exists between excess zinc and formation of amyloid plaques, with an imbalance of zinc a hallmark of the AD brain. Zinc promotes aggregation of endogenous Aβ in CSF in low concentrations and inhibits Aβ-mediated hydrogen peroxide production (Shcherbatykh and Carpenter 2007).

28.6.3 Genetic Disorders of Copper Metabolism

28.6.3.1 Menkes Disease

The neurological features of Menkes disease are present in early infancy, with impaired copper transport into and within the developing brain resulting in demyelination and neurodegeneration, revealing the critical role for MNK and copper in neuronal development (Madsen and Gitlin 2007). Menkes disease is an X-linked disorder characterized by growth failure, brittle hair, hypopigmentation, arterial tortuosity, and neuronal degeneration due to a loss-of-function mutation in the gene encoding the copper transporter Atp7a (MNK). Neuropathological exam reveals a focal degeneration of gray matter and neuronal loss most prominent in hippocampus and cerebellum, with decreased myelination with cerebellar and cerebral atrophy as revealed by MRI (Madsen and Gitlin 2007).

28.6.3.2 Wilson Disease

Wilson disease is an autosomal recessive disorder leading to cirrhosis of the liver and progressive neurodegeneration in the basal ganglia as a result of a loss-of-function mutation in the gene encoding the copper transporter Atp7b (WND) (Madsen and Gitlin 2007). Wilson disease is characterized by impairment in the biliary excretion of copper, leading to hepatocyte copper accumulation, copper-mediated liver damage, apoptosis, leakage of copper into plasma, and copper overload in extrahepatic tissues due to excess accumulation from the plasma following liver injury. Half of the patients with Wilson disease present with signs and symptoms of neuropsychiatric illness, with brain copper accumulation during Wilson disease leading to dystonia, dysarthria, and other Parkinsonian symptoms, as well as psychiatric symptoms of depression, cognitive deterioration, personality change, psychosis, and schizophrenia (Madsen and Gitlin 2007).

Summary Points

- Trace elements are required for proper biological functioning, but homeostasis must be strictly regulated to prevent oxidative damage and neurodegeneration.
- Iron is required for oxidative phosphorylation, nitric oxide metabolism, and oxygen transport.
- Manganese is required for normal immune function, regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, defense against free radicals, and blood clotting in concert with vitamin K.
- Copper is required for cellular respiration, iron oxidation, and pigment formation, neurotransmitter biosynthesis, antioxidant defense, peptide amidation, and connective tissue formation.
- Zinc is required for protein synthesis, all stages of metabolism, synaptic activity, and neuronal function.
- Iron, manganese, copper, and zinc play a critical role in brain development, with metal deficiencies or toxicities during embryogenesis deleterious.
- Iron, manganese, copper, and zinc are essential for proper neurotransmitter biology, influencing synaptic function and neurotransmitter receptor and transport proteins.
- Deficiencies of essential trace metals can have deleterious effects of the functioning of central nervous system, leading to learning deficits and neurodegeneration.
- Overload or toxic levels of trace metals can lead to production of reactive oxygen species, oxidative damage, and neural dysfunction.
- Neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease have been linked to altered brain homeostasis of trace metals such as iron, manganese, copper, and zinc.

Key Terms

Biogenic amine: A biologically active neurotransmitter than contains an amine group.
Blood-brain barrier: A selectively permeable barrier formed by the tight junctions of vascular endothelial cell membranes and astrocytes in the brain; this barrier protects the brain from exogenous molecules; most metabolites and molecules require a specific protein transporter for trafficking across the membrane.
Blood-cerebrospinal fluid barrier: A barrier formed in the choroid plexus of the brain between the cerebral capillaries and the extracellular space containing the cerebrospinal fluid; metabolites, molecules, and toxins may enter the brain through this barrier.
Catecholamine: A classical neurotransmitter that contains a catechol group and an amine group; includes dopamine, norepinephrine, and serotonin.
Ceruloplasmin: A copper-containing protein essential for copper transport and regulation of intracellular copper concentrations that act as a ferroxidase in the brain.
Ferritin: An iron-storing protein composed of a heavy and light chain that regulates intracellular iron concentrations.
Glial cell: a cell within the central nervous system that supports the activity and function of neurons; glial cell types include astrocytes, oligodendroglia, and microglia.
Metalloenzyme: A catalytic protein enzyme that contains one or more metal ions or requires metal ions as a cofactor in order to function.
Metallothionein: A cysteine-rich protein that binds and sequesters metal ions in the cell to prevent cytotoxicity and cellular damage.
Transferrin: A glycoprotein that binds iron for transport in the bloodstream and inside cells; may also bind and transport other metals such as manganese.

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References

Anderson JG, Cooney PT, Erikson KM. Environ Toxicol Pharmacol. 2007;23:179–84.
Anderson JG, Fordahl SC, Cooney PT, Weaver TL, Colyer CL, Erikson KM. Neurotoxicology. 2008;29:1044–53.
Arredondo M, Núñez MT. Mol Asp Med. 2005;26:313–27.
Aschner M, Erikson KM, Dorman DC. Crit Rev Toxicol. 2005;35:1–32.
Autissier N, Rochette L, Dumas P, Beley A, Loireau A, Bralet J. Toxicology. 1982;24:175–82.
Beard JL, Connor JR, Jones BC. Nutr Rev. 1993;51:157–70.
Beard JL, Wiesinger JA, Jones BC. Brain Res. 2006;1092:47–58.
Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, et al. Nutr Neurosci. 2005;8:31–8.
Cornett CR, Markesbery WR, Ehmann WD. Neurotoxicology 1998;19:339–345.
Crossgrove J, Allen D, Bukaveckas B, Rhineheimer S, Yokel R. Neurotoxicology. 2003;24:3–13.
Cuesta de Di Zio MC, Gomez G, Bonilla E, Suarez-Roca H. Life Sci. 1995;56:1858–64.
Dineley KE, Votyakova TV, Reynolds IJ. J Neurochem. 2003;85:563–70.
Donnelly PS, Xiao Z, Wedd AG. Curr Opin Chem Biol. 2007;11:128–33.
Erikson KM, Thompson K, Aschner J, Aschner M. Pharmacol Ther. 2007;113:369–77.
Eriksson H, Gillberg PG, Aquilonius SM, Hedström KG, Heilbronn E. Arch Toxicol. 1992;66:359–64.
Fitsanakis VA, Aschner M. Toxicol Appl Pharmacol. 2005;204:343–54.
Fujita M, Itakura T, Takagi Y, Okada A. J Parenter Enteral Nutr. 1989;13:421–5.
Gaasch JA, Lockman PR, Geldenhuys WJ, Allen DD, Van der Schyf CJ. Neurochem Res. 2007;32:1196–208.
Gingrich KJ, Burkat PM. J Physiol. 1998;506:609–25.
He L, Girijashanker K, Dalton TP, Reed J, Li H, Soleimani M, et al. Mol Pharmacol. 2006;70:171–80.
Kerr DIB, Ong J. Pharmacol Ther. 1995;67:187–246.
Lai JCK, Lim L, Davison AN. J Inorg Biochem. 1982;17:215–25.
Macreadie IG. Eur Biophys J. 2008;37:295–300.
Madsen E, Gitlin JD. Annu Rev Neurosci. 2007;30:317–37.
McCall KA, Huang C, Fierke CA. J Nutr 2000;130:1437s–1446s.
McDougall SA, Reichel CM, Farley CM, Flesher MM, Der-Ghazarian T, Cortez AM, et al. Neuroscience. 2008;154:848–60.
Mergler D, Huel G, Bowler R, Iregren A, Belanger S, Baldwin M, et al. Environ Res. 1994;64:151–80.
Nakashima AS, Dyck RH. Brain Res Rev. 2009;59:347–73.
NAS (National Academy of Science), 2002. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, Zinc. Available at www.nap.edu/books/0309072794/html/.
Normandin L, Beaupré LA, Salehi F, St. Pierre A, Kennedy G, Mergler D, et al. Neurotoxicology. 2004;25:433–41.
Pal PK, Samii A, Calne DB. Neurotoxicology. 1999;20:227–38.
Reaney SH, Smith DR. Toxicol Appl Pharmacol. 2005;205:271–81.
Roels H, Lauwerys R, Genet P, Sarham MJ, de Fays M, Hanotiau I, et al. Am J Ind Med. 1987;11:297–305.
Rommelfanger KS, Weinshenker D. Biochem Pharmacol. 2007;74:177–90.
Sahni V, Léger Y, Panaro L, Allen M, Giffin S, Fury D, et al. Environ Health Perspect. 2007;115:1176–9.
Sandstead HH, Smith Jr JC. J Nutr. 1996;126:2410s–8.
Sandstead HH, Frederickson CJ, Penland JG. J Nutr. 2000;130:496s–502.
Shcherbatykh I, Carpenter DO. J Alzheimers Dis. 2007;11:191–205.
Siddappa AJM, Rao RB, Wobken JD, Casperson K, Leibold EA, Connor JR, et al. Pediatric Res. 2003;53:800–7.
Struve MF, McManus BE, Wong BA, Dorman DC. Am J Ind Med. 2007;50:772–8.
Szewczyk B, Poleszak E, Sowa-Kucma M, Siwek M, Dudek D, Ryszewska-Pokrasniewicz B, et al. Pharmacol Rep. 2008;60:588–99.
Takeda A. Brain Res Rev. 2003;41:79–87.
WHO/UNICEF/UNU. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. Geneva: World Health Organization; 2006.
Youdim MBH, Ben-Shachar D, Yehuda S. Am J Clin Nutr. 1989;50:607–17.
Youdim MB. Nutr Rev. 2001;59:83–7.