Chapter 149
Dietary Zinc and the Brain

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Abbreviations

AD	Alzheimer's disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ATP/ADP	Adenosine tri/di phosphate
BBB	Blood brain barrier
CSF	Cerebrospinal fluid
CNS	Central nervous system
ECF	Extracellular fluid
ER	Endoplasmic reticulum
MAPK	Mitogen activated protein kinase
MT	Metallothionein
RDA	Recommended daily allowance
UIL	Upper intake level
VGCC	Voltage-gated Ca^{2+} channels
(S)VZ	(Sub)Ventricular zone
ZIP	Zn^{2+} importing proteins
[Zn]	Concentration of Zn
ZnT	Zn transporter

149.1 Introduction

The physiological importance of zinc (Zn) was first recognized in 1940 when the Zn-containing enzyme, carbonic anhydrase, was described (Keilin and Mann 1940). Eventually, Zn was recognized as an 'essential' trace element found widely distributed in all human organs and tissues and required for the structure and functions of many cellular proteins (Table 149.1). Today, the importance of Zn in human health is well documented (Frederickson et al. 2005; Maret and Sandstead 2008). In the brain, Zn plays important roles both in its development and function.

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Table 149.1 Key facts on zinc

Chemistry and physical properties

- Discovery: German chemist Andreas Sigismund Marggraf (1746) is normally given credit for discovering pure metallic Zn.
- Avaialability: the 24th most abundant element on the Earth's crust
- Empirical formula: Zn
- Position in the periodic table: 1st element in group 12
- Number of stable isotopes: five
- Atomic number: 30
- Atomic weight: 65.39 g

Uses

- Zinc plating for corrosion-resistance (e.g. on steel).
- Zinc alloys such as brass (alloy of zinc and copper) is used in batteries.
- Zinc chloride in deodorants
- Zinc pyrithione in shampoos
- Zinc sulfide in luminescent paints
- Zinc-carbonate, Zn-gluconate as dietary supplements

Biological importance

- Considered an essential mineral
- Structural component of many enzymes such as alcohol dehydrogenase in humans or other biomolecules important in cellular and molecular processes such as Zn finger transcription factors.
- Half of the total body's Zn is present in muscle. Other major organs of the body that contain zn includes bones, skin, kidneys, testes, and prostate glands
- Zinc deficiency causes growth retardation, delayed sexual maturation, infection susceptibility, and diarrhea, etc.
- Zinc excess is associated with ataxia, lethargy, and copper and iron deficiency.

This table includes the key facts on Zn including its chemical properties, uses, and biological importance

Zinc metalloproteins are the major (~80%) reservoir of the total brain Zn while the rest is free Zn^{2+} and are histochemically detectable by Timm's sulfide-silver staining method (Frederickson and Danscher 1990). In the brain, Zn is relatively concentrated in the hippocampus and amygdala (Takeda et al. 2004). Both regions are enriched with histochemically reactive Zn^{2+} which predominantly exists in the presynaptic vesicles. Zinc homeostasis in the brain is maintained by the blood brain barrier system and is not easily disrupted by dietary Zn deficiency. Nevertheless, histochemically detectable Zn in hippocampus are susceptible to dietary Zn deficiency.

Most of the cells in the human body including neuron maintain Zn homeostasis through the regulated expression of proteins for Zn- import, export, and sequestration. Specific Zn transporters are used in certain tissues and their expression may vary with dietary Zn status and time (Dufner-Beattie et al. 2003; Kelleher and Lonnerdal 2003). Thus Zn homeostatic mechanisms appear to be tissue specific.The mechanism of exact regulation of Zn uptake from extracellular fluids (ECF) into neurons and glial cells, however, is not completely known.

Large numbers of the world's population, an estimated total of about 50%, are at risk of Zn deficiency (Brown et al. 2001). Zinc deficiency in children is a nutritional and health concern in both developing and developed countries (Black 1998; Bryan et al. 2004). Zinc deficiency results in decrease in extracellular [Zn] in the hippocampus which subsequently causes abnormal glucocorticoid secretion from the adrenal cortex. As the hippocampus is enriched with glucocorticoid receptors, the abnormal glucocorticoid secretion alters its function. Abnormal glucocorticoid secretion in Zn deficiency is associated with neuropsychological symptoms affecting cognitive performance and aggravated glutamate excitotoxicity. The decrease in Zn^{2+} pool in the peripheral tissue in Zn deficiency can also change glucocorticoid action by triggering abnormal glucocorticoid secretion.

Alterations in Zn homeostasis in the brain is observed in Parkinson's and Alzheimer's disease (AD) as well as in transient forebrain ischemia, seizures, and traumatic brain injury. There is much evidence to show that amyloid-beta deposition in AD is induced by Zn (see review Mocchegiani et al. 2005). An elevated concentration of Zn or an excess of Zn in the brain might play a role in such pathological conditions. Indeed the exact neuropathological mechanism of either the elevated level of Zn^{2+} or its deficiency has not been completely resolved (Colvin et al. 2003; Sensi et al. 2009).

This chapter will elaborate on the physiological importance of dietary Zn in the brain. Emphasis will be given to the mechanism of Zn homeostasis, the role of dietary Zn in brain development, and the consequences of Zn excess and/or Zn deficiency in brain pathology.

149.2 Dietary Sources of Zn and Its Bioavailability

The richest food sources of Zn (Table 149.2) are sea foods (shellfish, shrimp, lobster, crab-meat), organs and flesh of mammals and fowls (liver, meat), whole grain cereals, and some beans (Brown and Begin 1993). The total Zn content of the diet and its bioavailability, solubility in particular, in the intestinal lumen determines the amount of Zn absorbed and which can be utilized or metabolized in different organs. This also is influenced by the chemical form of Zn and the presence or absence of specific enhancers or inhibitors of Zn absorption. Amino acids such as cysteine and histidine can increase the solubility of Zn. However, some proteins such as casein have an inhibitory effect on Zn absorption. Myoinositol hexaphosphate (phytate) reduces Zn bioavailability (Soto-Quintana et al. 2003), and therefore oils, fats, and sugar are not considered good sources of Zn. Meal proteins have a positive effect on Zn absorption. In humans without excessive intake of Zn, the body burden half-time of absorbed Zn has been observed in the range between 162–500 days. After parenteral administration, half-times of Zn may vary within the range of about 100–500 days (see review Lowe et al. 2009). In spite of its great importance in human health, the amount of zinc in the diet, however, needs to be maintained properly (Table 149.3).

149.3 Blood Brain Barrier and Permeability of Zn in Brain

Both the supply of the required nutrients for proper functioning of the brain and the control of harmful substances present in the bloodstream so as to prevent them from entering the brain are done by the specialized system of capillary endothelial cells of the blood brain barrier (BBB). The transport

Table 149.2 Zinc in human diet (From Brown and Begin 1993)

Category of foods	Example of edibles
Major dietary source of Zn	
Sea foods	flesh of shellfish, shrimp, lobster, crab
Organs and flesh of mammals and fowls	liver, meat, or muscle
Whole grain cereals, vegetables	chickpeas, kidney beans, almonds
Dairy products	yogurt, milk, cheese
Inhibitors of Zn absorption	Casein
Protein	Plant oil
Oils or fats	Sugar
Carbohydrate	

Zinc is available in various food and food products. This table includes a partial list of the dietary sources of Zn. The amount of Zn, however, may vary depending on type and species

Table 149.3 Recommended daily allowance (RDA) and upper intake levels (UIL) for human Zn consumption (From Institute of Medicine, Food and Nutrition Board. Washington, DC: National Academy Press, 2001)

	For male	For female	In pregnancy	During lactation
Age	RDA/UIL	RDA/UIL	RDA/UIL	RDA/UIL
0–6 months	2 mg/4 mg	2 mg/4 mg		
7–12 months	3 mg/5 mg	3 mg/5 mg		
1–3 years	3 mg/7 mg	3 mg/7 mg		
4–8 years	5 mg/12 mg	5 mg/12 mg		
9–13 years	8 mg/23 mg	8 mg/23 mg		
14-18 years	11 mg/34 mg	9 mg/34 mg	13 mg/34 mg	14 mg/34 mg
19+ years	11 mg/40 mg	8 mg/40 mg	11 mg/40 mg	12 mg/40 mg

Both the recommended amount of dietary Zn or Zn supplement and upper tolerable levels vary depending on age, gender, or stage of growth and development. This table includes the amount of Zn recommended for daily consumption and the maximum or upper tolerable limit (UIL) for different ages or conditions to maintain optimum health

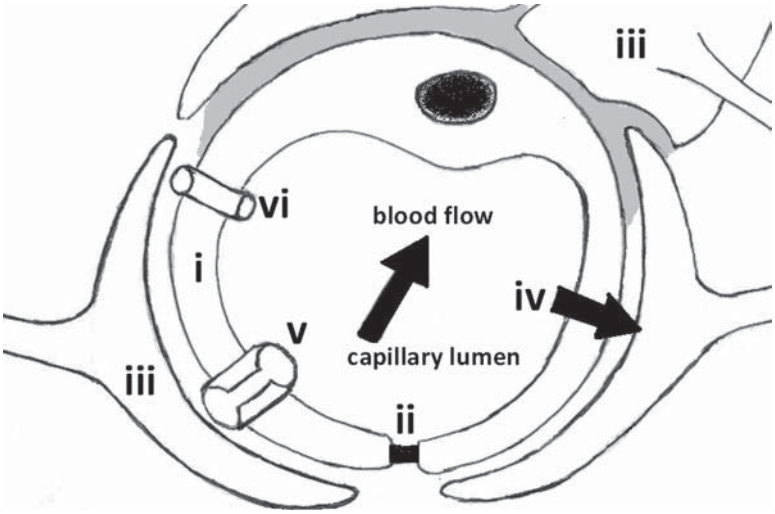

Fig. 149.1 The blood-brain barrier controls the exchange of ions including zinc, amino acids, peptides, and other substances between blood and brain. At the brain blood capillaries, the endothelium cells (i) are joined together at their edges by tight junctions (ii),which prevent water-soluble substances in the blood to enter the CSF. Most of the areas of the blood capillaries are enclosed by the astrocyte's "end-feet" (iii). Thus water-soluble substances can cross the BBB by passing directly through the walls of the cerebral capillaries made up of a lipid/protein bilayer. Fat-soluble molecules, including O_2 and CO_2, anesthetics and alcohol can pass straight through the lipids in the capillary walls (iv). Ions and amino acids can pass through using carrier proteins such as zinc import proteins (v), ion channels or pumps (vi) (Modified from Springer Image library accessed on 01 January, 2010 from http://www.springerimages.com/Images/Pharmacy/1-10.1208_s12248-008-9018-7-0)

of Zn into the brain parenchyma occurs via the BBB system (Kahn 2005). Entry of Zn into the brain is allowed through different kinds of proteins and channels on the BBB (Fig. 149.1). In other words the BBB system provides a strict regulation on Zn homeostasis in the brain and is not easily disrupted by dietary Zn (Franklin et al. 1992).

The presence of specific Zn transport sites on the brain capillary endothelial cells (Buxani-Rice et al. 1994) confirms the important regulatory role of the BBB in brain Zn homeostasis. The BBB-mediated control of Zn homeostasis in the brain is also supported by the enhanced transport of Zn across the BBB, as shown by an in vitro model of the BBB that was exposed to Zn-deficient conditions. The rate of Zn transport across the in vitro BBB model constructed using cultured porcine brain

capillary endothelial cells on porous membrane was observed to be slower when [Zn] was below 7 μmol/L and faster when it was above 30 μmol zinc/L (Lehmann et al. 2002). Notably, the zinc transport process is highly selective for Zn since none of the analogous minerals could effectively compete with zinc; besides, the zinc transfer process does not require much energy. Furthermore, metabolic inhibitors also do not influence the transport rate (Bobilya et al. 2008).

In order to maintain Zn homeostasis, brain capillary endothelial cells respond to changes in Zn status, increasing the uptake of Zn in the presence of low [Zn] in the blood and decreasing it in the presence of high [Zn] in the blood (Lehmann et al. 2002). Following its uptake, Zn can be transferred freely through the CSF and the brain ECF compartments. The reduced amount of histochemically reactive Zn in Zn deficiency suggests its reduced uptake in Zn deficiency (Takeda 2001).

149.4 Homeostasis of Zn in the Brain and Dietary Influence

The variation in the amount of Zn in different regions of the mammalian central nervous system (CNS) varies over about a fivefold range, with lower amounts generally in white matter (26–40 ppm in cortical white matter) and higher amounts in grey matter (60–90 ppm in cortical grey matter). On an average, the estimated amount of Zn in one gram of wet brain tissue is about 10μg corresponding to an average total intracellular [Zn] of about 150μM. This concentration is about 10-fold more than the serum [Zn]. On the regional distribution within the brain, the estimated total [Zn] in the hippocampus is more than 200 μM (see review Takeda and Tamano 2009), considered the highest compared to any other region (Frederickson et al. 2005). Notably, hippocampal [Zn] can be decreased significantly in dietary Zn deficiency. Among the other regions, the amygdala and neocortex contain the highest amount of Zn (Fig. 149.2).

In the ECF of the brain, Zn is either bound to low molecular weight ligands such as metalloproteins, or stay as free Zn^{2+} (see review Takeda and Tamano 2009). In the ECF, the estimated total [Zn] and

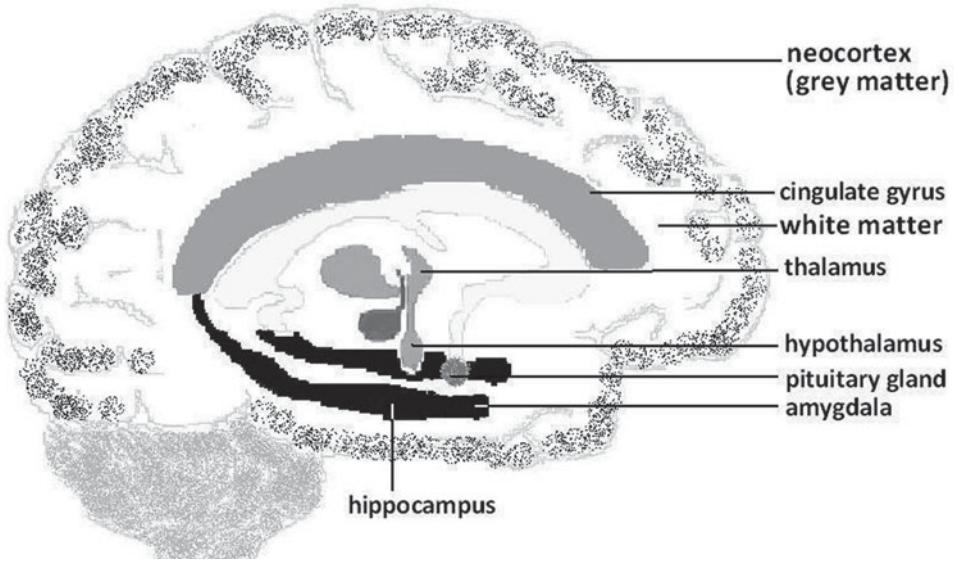

Fig. 149.2 Human brain-zinc map. The hippocampus belongs to the limbic system containing the highest concentration of zinc in the brain (*dark black area*). Other regions of the brain that contain relatively higher amount of Zn is the amygdala (*dark black area*) and grey matter neocortex (*black dotted area*)

free [Zn^{2+}] are 0.15–1 μM (Hershey et al. 1983; Weiss et al. 2000) and ~5–20 μM (Frederickson et al. 2006) respectively. About 80% of the total brain Zn is bound with Zn metalloproteins while the rest is histochemically detectable using Timm's sulfide-silver staining method (Frederickson and Danscher 1990). This is based on the observation that the removal of Zn transporter protein results in a 20% reduction of the total amount of Zn in the brain (Cole et al. 1999).

Within the brain, both the extracellualr and intracellular Zn are exchangeble. Extracellular Zn^{2+} in the brain may change because of its release from cells (Frederickson 1989; Qian and Noebels 2005), while changes in intracellular Zn^{2+} may result from oxidative stress (Frazzini et al. 2006). The concentration of rapidly exchangeable cytosolic free Zn^{2+} is estimated in the subnanomolar level. Such dynamic changes in Zn^{2+} gradients and the availability of specific Zn^{2+} binding domains suggest the importance of Zn^{2+} ions as signaling molecules. However, the signaling effects of Zn^{2+} may be mediated by intracellular or extracellular Zn^{2+} (Sensi et al. 1997).

In Zn deficiency, the level of serum Zn decreases which in turn leads to a decrease in CSF Zn. Although one week of Zn deprivation in young rats can decrease serum Zn level about 50% compared to control animals, a significant change (decrease) in extracellular Zn in the hippocampus is observed only after 4 weeks of Zn deprivation. Histochemically reactive Zn (Timm's stain) also decreases after 4 weeks of Zn deprivation. Thus only a prolonged period of Zn deficiency (4 weeks in contrast to 1 week) can cause a decrease in hippocampal Zn. Notably, extracellular Zn may lead to the decrease in histochemically reactive Zn. Extracellular Zn is also responsive to dietary Zn deficiency in other regions such as the amygdala, followed by a decrease in histochemically reactive Zn (Takeda and Tamano 2009).

The protein-bound Zn in intracellular compartments of the brain, on the other hand, may be resistant to Zn deficiency. It is possible that the response of hippocampal Zn to dietary Zn deficiency reflects that of peripheral Zn since the decrease in serum Zn may lead to the reduction of Zn^{2+} pool in peripheral tissues. It is possible that insufficient Zn^{2+} signaling in peripheral tissues is associated with activation of the hypothalamo-pituitary-adrenocortical system in Zn deficiency (Takeda and Tamano 2009).

149.5 Transport and Homeostasis of Zn in Neuron and Dietary Influence

Cells in different parts of the brain have different amounts of Zn which in turn contributes to the variable amount of Zn in different brain areas. The free [Zn^{2+}] in the cytosol from cultured neurons is estimated at subnanomolar (Weiss et al. 2000). However, Zn content in the synaptic vesicles of some neurons in the forebrain is found to be approximately >1 mM (Frederickson et al. 2005). Although intraneuronal cytosolic Zn^{2+} is in the subnanomolar or picomolar range, it is estimated to rise to micromolar levels in the proximity of axon terminals following release from synaptic vesicles that contain Zn^{2+} at millimolar range (Frederickson et al. 2005). This is most likely also the case in other intracellular compartments such as mitochondria, vesicles, and lysosomes that can take up cytosolic Zn^{2+} (Sensi et al. 2003; Colvin et al. 2006; Hwang et al. 2008; Dittmer et al. 2009).

Neurons that contain free Zn^{2+} in the vesicles of their presynaptic boutons are present both in forebrain areas (such as hippocampus, amygdala, and neocortex) and other areas of the brain (Fig. 149.2). Those neurons in the forebrain area are a subgroup of excitatory glutamatergic (or gluzinergic) neurons and in other areas they are termed Zn-enriched neurons (Frederickson and Danscher et al. 1990). Since the distribution of these neurons within the brain is not uniform, Zn distribution in the brain is also not uniform.

The exact mechanism that regulates Zn uptake from the ECF into neurons and glial cells is still not completely known. Most of the cells maintain Zn homeostasis through the regulated expression of proteins for Zn import, export, and sequestration (Table 149.4). Furthermore, Zn homeostatic

Table 149.4 Zn^{2+} transport and storage in neurons

Zn transporter(s) or storage protein	Important features
VGCCs and Ca^{2+}/Zn^{2+}-permeable AMPA receptors	Located at the plasma membrane the main routes Zn^{2+} entry into neurons
ZnT1	Located at the plasma membrane controls Zn^{2+} efflux interacts with the L-type VGCC that regulates Ca^{2+} and Zn^{2+} influx.
ZnT3	Located at the synaptic vesicles
ZnT5, ZnT6, ZnT7	Located at the golgi apparatus
ZnT5, ZnT6, ZnT7	Located at the lysozome
The Na^{s}/Zn^{2+} exchanger	Moves Zn^{2+} in or out of neurons depending on the Na^{+} gradient
ZIP	H^{+}- or HCO_3-Zn^{2+} co-transporters and facilitates Zn^{2+} influx.
Ca^{2+} uniporter	Located at mitochondria
MT (MT-III)	Major Zn^{2+}-homeostatic proteins in neurons

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; MT, metallothionein VGCCs, voltage-gated Ca^{2+} channels; ZIP, Zinc importing protein

This table summarizes the list of major zinc transporters involved in supply and homeostasis of zinc in neurons (for detail see Ohana et al. 2009)

mechanisms appear to be tissue specific. Specific Zn transporters are used in certain tissues and its expression varies with dietary Zn status and time (Dufner-Beattie et al. 2003; Kelleher and Lonnerdal 2003). A number of Zn^{2+} transporters (ZnTs), Zn^{2+}-importing proteins (ZIPs), and buffering proteins such as the metallothioneins (MT) bind cytosolic Zn^{2+} and mediate the complex intraneuronal cytosolic Zn^{2+} homeostasis. In addition, specific gated Zn-permeable membrane-spanning channels, such as voltage-gated L-type Ca^{2+} channels, Na^{+}/Zn^{2+} exchangers, N-methyl-D-aspartate (NMDA) receptor gated channels, and Ca^{2+} permeable AMPA/kainate channels can also mediate the neuronal uptake of Zn. Zinc transporter proteins too regulate the efflux of Zn from neurons as well as vesicular Zn uptake. Transporters of the Zip family, which are the main membrane Zn uptake transporters, also seem to be involved in this process (reviewed in Ohana et al. 2009).

ZnTs mediate Zn^{2+} transport from the cytosol to the lumen of intracellular organelles or out of the cell. There are at least ten members of the ZnT family, most of which are ubiquitously expressed, except ZnT3 which is neuron specific and present on synaptic glutamatergic vesicles. With the exception of ZnT1, ZnTs are present on intracellular organelles such as the Golgi and the secretory vesicles of many organs (Table 149.4). Zinc Transporter 1 is expressed, synaptically and extrasynaptically, on the plasma membrane of neurons and glia. Other ZnT family members, ZnT2, ZnT4, ZnT5, and ZnT6, are also expressed in several brain regions (reviewed in Sensi et al. 2009) such as in the hippocampus, cortex, and olfactory bulb (Lee et al. 2003), and in certain cerebellar GABAergic and dopaminergic neurons (Ruiz et al. 2004). Zin Transporter 7, which probably facilitates Zn^{2+} transport from the cytoplasm into the Golgi apparatus, is moderately expressed in the brain and ZnT2, ZnT5, and ZnT6, which are associated with vesicular Zn uptake and Zn efflux in many organs, should similarly play a minor role in the brain.

149.6 Biochemistry of Zn Binding with Proteins in Brain

The knowledge of the biochemical importance of Zn dates back to 1940 with the discovery of the Zn-containing enzyme, *carbonic anhydrase*, now known to contain 1 gram atom of the metal per mole (Keilin and Mann1940). Subsequently, more than 300 such Zn containing proteins with catalytic,

structural, and other functional roles have been described. This number is more than that of any other transition or Group IIB metal (Vallee and Falchuk 1993) that is involved in biomolecules. Specific binding sites for Zn^{2+} are present on numerous proteins, including Zn^{2+} fingers on transcription factors that bind it with high affinity, and metallothioneins, from which the Zn^{2+} is easily dissociable.

Zinc binds to many proteins involved in gene regulation. The Zn finger proteins as transcription factor, Zn twists in steroid receptors, and Zn clusters in the galactose metabolism activator are well known examples. Other metalloproteins tightly binding Zn include the RING finger protein family (Freemont 1993), the tumour suppressor p53, the human growth hormone-prolactin receptor complex, and metallothionein proteins (Ebadi 1986; Vallee and Falchuk 1993). Zinc also stabilizes the 3D structure of superoxide dismutase (Salguerio et al. 2007). A partial list of Zn finger transcription factors present in different areas and types of cells in the brain is given in Table 149.5. In the brain, Zn is structurally important for reelin, a large secreted protein, implicated in the cortical development of the mammalian brain. A 2.0-Å crystal structure from the fifth and sixth reelin repeats fragment revealed the presence of Zn^{2+} bound to them (Yasui et al. 2007).

The biochemical importance of Zn lies in its role as catalytic, coactive (or co-catalytic), structural (Vallee and Falchuk 1993; MacDonald 2000), and intracellular signaling factor such as the regulation of

Table 149.5 Zinc finger transcription factors in the brain

Transcription factor	Expression site and/or function
ATBF1	• Protein is highly expressed in the midbrain and diencephalon • mRNA is highly expressed in the brainstem, mostly in embryo and neonatal brain, postmitotic neurons in the brainstem • Expression is transient and weak in the precursor cells at early neurogenesis. • Expression decreases postnatally, but remains in mature neurons • Regulation of neuronal cell maturation or region-specific central nervous system differentiation
Bcl11A/Evi9/CTIP1	• Bcl11A-S/Evi9c is widely expressed in different regions of the rat brain • Bcl11A-L/Evi9a is expressed in the cerebral cortex, hippocampus, and olfactory bulb
DRRF (Sp1 family of transcription factors)	• Highly expressed in the neural ectoderm and neural groove • Moderately expressed in the mesoderm and endoderm at the early embryonic stage. • Highest DRRF mRNA levels in olfactory bulb and tubercle, nucleus accumbens, striatum, hippocampus, amygdala, and frontal cortex. • Regulates dopaminergic neurotransmission
Egr3	• Expressed in cortex and colocalized with zif268. • Important in defining long-term, neuroplastic responses.
FOG-2	• Expressed in developing and adult heart, brain, and testis • Important cofactor for GATA-mediated transcriptional activation in cardiac and neural cell lineages.
Ik-1 and Ik-2	• Positive regulators of enkephalin gene expression in the developing striatum • Participate in regulating enkephalinergic differentiation
Lot1	• High in cerebellar granule cells, a neuronal population undergoing postnatal neurogenesis
MOK2	• *PAX3* and *IRBP* (interphotoreceptor retinoid-binding protein) genes are two potentially important target genes for the MOK2 protein.
NSM1(IA-1)	• In mouse brain, *Insm1* is strongly expressed for 2 weeks after birth but shows little or no expression thereafter. • During embryo development Cbl-associated protein may enter the nucleus through its own nuclear localization signal or by binding to INSM1.

(continued)

Table 149.5 (continued)

Transcription factor	Expression site and/or function
Plag1, Plag-l2	• In the CNS and PNS • In olfactory and neuroendocrine lineages. • Might control cell fate and proliferation decisions in the developing nervous system (Oncogenes)
REST/NRSF/XBR	• Highest levels in the neurons of hippocampus, pons/medulla, and midbrain • A negative regulator rather than a transcriptional silencer of neuronal gene expression and counteracts with positive regulators to modulate target gene expression quantitatively in different cell types, including neurons.
RP58	• mRNA at E 10 in the neuroepithelium, and subsequently in the VZ of the cerebral cortex in the E12 embryo. • Strong expression in the preplate in the cerebral cortex from this stage onward. High levels of expression continue to be detected in the cortical plate and SVZ of the neocortex, hippocampus, and parts of the amygdala
Sp8	• Expressed in neurogenic regions, which gives rise to olfactory bulb interneurons at embryonic and postnatal time points and remains expressed in the calretinin-expressing and GABAergic/nondopaminergic interneurons of the glomerular layer. • Contributes to olfactory bulb interneuron diversity by regulating the survival, migration, and molecular specification of neuroblasts/interneurons.
Wt1	• The developing olfactory epithelium
Zac1(Plag family)	• Abundantly expressed in many neuroepithelia during early brain development • Regulates both apoptosis and cell cycle arrest (tumor suppressors)
Zfp423	• Expressed within the cerebellum, both in ventricular and external germinal zones. • Loss of Zfp423 results in diminished proliferation by granule cell precursors in the external germinal layer, especially near the midline, and abnormal differentiation and migration of ventricular zone-derived neurons and Bergmann glia
Zic1–5	• Precursor cells of the granule neuron and the neurons in cerebellar nuclei • Neurulation, neuronal differentiation, neural crest specification, the establishment of left-right asymmetry, and regulation of cell proliferation
Zif268 (Egr1)	• Zif268 is constitutively expressed in several parts including the temporal lobe. • Zif268 regulates neurological genes and cellular growth and proliferation genes. • Expressed in mammalian neurons during visual and fear learning, as well as in song learning in birds. • Expressed in response to cellular growth and proliferation signals by enhancing the expression of TGFβ1
ZNF536	• Most abundant in the developing central nervous system and dorsal root ganglia and localized in the cerebral cortex, hippocampus, and hypothalamic area. • Negatively regulates neuron differentiation.

This table includes a partial list of Zn finger transcription factors expressed in different sites and/or cells of the brain. Related functions of the respective transcription factors at the expression site are listed as well

cell proliferation (Hershfinkel et al. 2007). The catalytic roles of Zn include participating in the transformation of substrates by facilitating the formation of OH^- at neutral pH, or through Lewis acid catalysis. The structural role of Zn is mostly in stabilizing active tertiary peptide conformation. Notably, Zn^{2+} interacts strongly with electronegative sulfur, nitrogen, and oxygen moieties in multiple coordination geometries, and yet unlike Fe or Cu, it is not redox active under physiological conditions and thus does not promote the formation of toxic free radicals. As an extracellular signal factor Zn is involved in synaptic neurotransmission (Frederickson 1989; Vallee and Falchuk 1993). It is generally accepted that an increase in free intracellular Zn^{2+} is associated with cell death. For example, release of intracellular Zn^{2+}, triggered by formation of reactive oxygen species or by nitrosilation, induces proapoptotic molecules, e.g., p38, and activation of K^+ channels leading to cell death (McLaughlin et al. 2001; Pal et al. 2003).

149.7 The Developing Brain and Zn Status in Diet

The impact of Zn supplementation or a Zn-deficient human diet on brain development and function has not been consistent. Various dimensions of research design and a broad range of subjects varying in racial background, age, and food habits might have contributed to the observed inconsistency. However, a growing number of studies have shown the influence of maternal Zn on fetal growth and development (Goldenberg et al. 1995; Georgieff 2007; Cole and Lifshitz 2008). Daily Zn supplementation in women with relatively low plasma [Zn] in early pregnancy is associated with greater infant birth weights and head circumferences, with the effect occurring predominantly in women with a body mass index less than 26 kg/m^2 (Goldenberg et al. 1995). Very low birth weight of Canadian infants scored improved motor development when given Zn supplement (Friel et al. 1993) while low birth weight infants in Brazil (Ashworth et al. 1998) and older infants and toddlers in Guatemala (Bentley et al. 1997) and India (Sazawal et al. 1996) did not show changes in motor development. However, Zn supplementation to Zn-deficient mothers is important for proper brain development in neonates (Gibson 1994; Georgieff 2007). An adequate Zn nutriture is essential for optimal neurological development (Takeda 2001; Prasad 1997). Additional Zn intake during pregnancy results in increased neuronal proliferation in the ventricular zone of the developing brain (Azman et al. 2009). Regular consumption of more than the recommended intake, on the other hand, can have adverse effects (Ronowska et al. 2007).

149.8 Neurogenesis and Zn Supplement

Neurogenesis is a process to generate postmitoitc neuronal and glial cells from neuroepithelial stem cells. Proliferation, cell-cycle arrest, differentiation, migration, and the natural developmental death of neural precursors are well coordinated during neurogenesis (Moskowitz and Lo 2003). Optimal development of the brain depends on strict co-ordination of these events during neurogenesis. Various cell-cycle genes and transcription factors including Zn transcription factors expressed in neurons (Table 149.5) govern neurogenesis, which also determines the correct positional identity of the neural cells from the stem/progenitor cells (Araujo et al. 1990; Edenfeld et al. 2002). In most brain regions, the generation and proliferation of neurons is normally restricted to a discrete developmental period with exceptions for the regions such as hippocampus, dentate gyrus, and the subventricular zone (SVZ) of several species (Caviness 1973; Gueneau et al. 1982; Cameron et al. 1993; Kuhn et al. 1996; Gould et al. 1998; Eriksson et al. 1998; Doetsch et al. 1999), and almost all neurons are generated before early postnatal life and are generally not replaced with new ones (Rakic 1982). The ventricular zone (VZ) is the major site of proliferation and presumably produces all the cell types. A second proliferative zone, namely SVZ, also contributes large numbers of neurons to the developing cortex (Nowakowski and Rakic 1981). In addition, granule neurons are generated throughout life from a population of continuously dividing progenitor cells residing in the subgranular zone of the dentate gyrus in the rodent brain (Stanfield and Trice 1988; Kuhn et al. 1996).

In neuronal cells, Zn deficiency induces oxidative stress, alters the normal structure and dynamics of the cytoskeleton, affects the modulation of several transcription factors and induces a decreased cell proliferation and increased apoptotic death. Thus, Zn deficiency affects critical developmental events of neurogenesis (reviewed by Mackenzie et al. 2007; Nakashima and Dyck 2009). Zinc supplement on the other hand results in increased number of proliferating neurons in the VZ of the developing neocortex. This was observed in the mouse pups delivered by the mother given oral Zn supplement in drinking water during pregnancy (Azman et al. 2009). Notably, Zn is involved in

activation of enzyme systems that influence cell division and proliferation (Varrault et al. 1998; MacDonald 2000; Valente et al. 2005; Ronowska et al. 2007). During DNA synthesis, Zn affects thymidine kinase, the activity of which increases dramatically during the G1 and early S phases of the cell cycle. Zinc also influences the hormonal regulation of cell division. Insulin-like growth factor-I and the pituitary growth hormone axis are responsive to Zn status (Root et al. 1979; Roth et al. 1994).

149.9 Neuronal Apoptosis and Zn Deficiency

Zn deficiency was found to increase the expression of Zn transporters in the brain, which facilitates increased brain Zn uptake and results in the conservation of brain Zn during Zn deficiency (Chowanadisai et al. 2005). In neuronal cells, Zn deficiency induces oxidative stress, alters the normal structure and dynamics of the cytoskeleton, affects several transcription factors, and results in decreased cell proliferation and increased apoptosis. These closely associated events affect neuronal function and critical developmental events of neurogenesis when Zn availability decreases (Mackenzie et al. 2007).

In human neuronal cell model IMR-32 cells, a decrease in cellular Zn triggers mitogen-activated protein kinases (MAPKs) both in H_2O_2-independent and dependent manner. Cells grown in low Zn-containing media showed increased cell oxidants and H_2O_2 release, increased c-Jun N-terminal kinase (JNK) and p38 activation, high nuclear activator protein-1 (AP-1)-DNA binding activity, and AP-1-dependent gene expression. Increase in cellular H_2O_2 can trigger the activation of JNK and p38, leading to AP-1 activation, events that are not involved in Zn deficiency-induced apoptosis (Zago et al. 2005).

149.10 Zinc Deficiency or Excess and Brain Pathology

The homeostasis of the free Zn^{2+} pool and the mechanisms involved in controlling that homeostasis are pivotal for proper brain physiology. Acute human dietary deficiency is accompanied by CNS related Zn-reversible symptoms such as anorexia, smell and taste dysfunction, emotional and cognitive disturbances, and loss of coordination (Fig. 149.3) (Ashworth et al. 1998; Bhatnagar and Taneja 2001). Perhaps this is because Zn as a neuromodulator at excitatory synapses plays an important role in stress response and in the functionality of Zn-dependent enzymes contributing to maintaining brain compensatory capacity. Dietary Zn deficiency was also reported to affect learning and memory. Deficiency in Zn is also associated with attention deficiency/hyperactivity disorder. Age-related decline in brain functions and impaired cognitive performances could be related to dysfunctions affecting the intracellular Zn^{2+} availability (Golub et al. 1995; Takeda 2000; Takeda et al. 2008).

Zn deficiency causes abnormal glucocorticoid secretion from the adrenal cortex, which is observed prior to the decrease in extracellular [Zn] in the hippocampus. The functions of glucocorticoid receptor-rich hippocampus are changed by abnormal glucocorticoid secretion that in turn aggravates glutamate excitotoxicity in neurological diseases. Thus Zn deficiency elicits neuropsychological symptoms and affects cognitive performance (Fig. 149.3). It is possible that the decrease in Zn^{2+} pool in the peripheral tissues triggers abnormal glucocorticoid secretion. In other words, the decrease in Zn^{2+} pool may cooperate with glucocorticoid action in Zn deficiency.

Again, elevated [Zn] or Zn excess in the brain has a profound negative effect on neurological cells, which are highly susceptible to extremes in extracellular [Zn]. The exact neuropathological mechanism of elevated level of Zn^{2+} is still unclear; however, it is found to be related to the progression

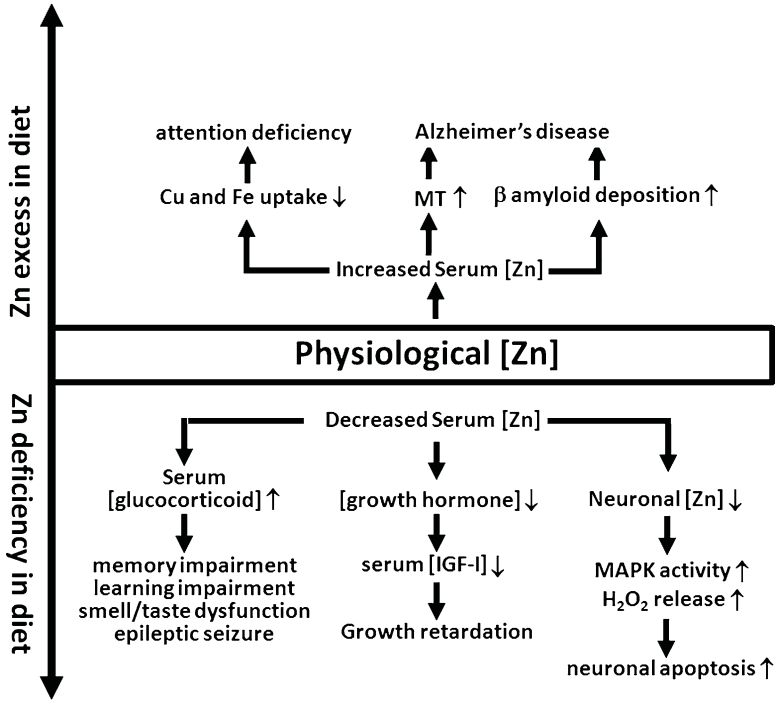

Fig. 149.3 Possible pathological consequences of dietary Zn-deficient or Zn-excess condition. In dietary Zn deficiency, serum [Zn] can be decreased leading to either increased serum glucocorticoid concentration or decreased growth hormone concentration or intracellular [Zn]. These conditions in turn may result in cognitive disturbances such as memory or learning impairment, growth retardation or neuronal apoptosis, respectively. In dietary Zn-excess condition, increased serum [Zn] can lead to decreased uptake of Cu and Fe in different organs, including the brain, or increased depositing of beta amyloid in the brain. *IGF* Insulin like growth factors I, *MAPK* mitogen activated protein kinase, ↓ decrease, increase

of AD and other neuropathologies (reviewed by Sensi et al. 2009). There is considerable evidence that amyloid-beta deposition in AD is induced by Zn, but the exact mechanism is still unclear (reviewd by Mocchegiani et al. 2005; Barnham and Bush 2008). An increased expression of MT-I and MT-II, and in some cases of MT-III (also known to be a growth inhibitory factor), is causally linked to such phenomena (Fig. 149.3). However, the protective roles of these proteins at a young age to maintain brain physiology and their functional ability in aging are not consistent. Alterations in Zn homeostasis have also been reported in Parkinson's disease as well as in transient forebrain ischemia, seizures, and traumatic brain injury. The altered Zn nutritional status of individuals with Down's Syndrome contributes to clinical complications that usually appear with their aging (Lima et al. 2010). Again, Zn metabolism is altered in the presence of Down's Syndrome (Licastro et al. 2001). Zinc supplement in diets has been tried to improve the patient's health albeit with conflicting results (Bucci et al. 2001; Blair et al. 2008).

149.11 Applications to Other Areas of Health and Disease

The importance of Zn in the biological system is remarkable and versatile. Zinc plays a pivotal role in gene expression involving cellular growth and differentiation; yet, unlike other transitional metals,

it does not cause any oxidative damage (Berg and Shi 1996). Enough is now known about the clinical and public health importance of Zn in human health and diseases. Community Zn supplementation programs among children in developing countries proved to have had a significant effect on the reduction of pneumonia (Bhutta et al. 1999). Zinc supplement has been beneficial for diarrhea prevention and childhood morbidity and mortality. Other than the brain (CNS), the epidermal, gastrointestinal, immune, skeletal, and reproductive systems are known to be affected clinically by severe Zn deficiency (Solomons 1998; Hambidge et al. 1986).

Summary Points

- The total Zn content of the diet and its bioavailability, especially its solubility in the intestinal lumen, determine the amount of absorbed Zn to be utilized or metabolized in the different organs including the brain.
- In the brain, Zn concentration is highest in the hippocampus which can decrease significantly in dietary Zn deficiency.
- The blood brain barrier system provides strict regulation on Zn homeostasis in the brain and is not easily influenced by dietary Zn.
- Zinc homeostasis is maintained through the regulated expression of proteins for Zn import, export, and sequestration.
- A multitude of Zn^{2+} transporters (ZnTs), Zn^{2+}-importing proteins (ZIPs), and buffering proteins such as the metallothioneins (MT) bind cytosolic Zn^{2+} and mediate the complex intraneuronal cytosolic free Zn^{2+} homeostasis.
- A number of Zn transcription factors are expressed in nerve cells and in different areas of the brain regulating genes involved in proliferation, differentiation, migration, and apoptosis of neurons and other cells of the brain.
- As an extracellular signal factor Zn is involved in synaptic neurotransmission.
- Additional Zn intake during pregnancy can increase neuronal proliferation at the ventricular zone of the developing brain.
- In neuronal cells, Zn deficiency induces oxidative stress, alters the normal structure and dynamics of the cytoskeleton, affects the modulation of transcription factors AP-1, NF-betaB, and NFAT and induces decreased cell proliferation and increased apoptotic death.
- Acute human dietary deficiency is accompanied by symptoms such as anorexia, smell and taste dysfunction, emotional and cognitive disturbances, and loss of coordination. Dietary Zn deficiency also has been reported to affect brain functions, including learning and memory defects.

Key Terms

Apoptosis: A form of cell death (or cell suicide) in which a programmed sequence of events leads to the elimination of cells without leaving or releasing harmful substances into the surrounding area of the dying cell(s). Apoptosis also refers to the structural changes that the cells undergo before the programmed death. Apoptosis is crucial in developing and maintaining health by eliminating old, unnecessary, and unhealthy cells. Hyperactivation and inactivation of apoptosis may result in pathological conditions. Hyperactivation may kill too many cells and inflict grave tissue damage, leading to such neurodegenerative disorders as Alzheimer's, Huntington's, and Parkinson's diseases.

Astrocyte: Astrocytes (collectively known as astroglia) are characteristic star-shaped glial cells in the CNS. Three forms of astrocytes exist in the CNS: *fibrous* (located in white matter and that physically connect the cells to the outside of the capillary wall when they are in close proximity to them), *protoplasmic* (found in grey matter tissue; they possess a larger quantity of organelles and exhibit short and highly branched cellular processes), and *radial* (disposed in a plane perpendicular to the axis of ventricles). Their functions include: biochemical support to the endothelial cells at the BBB, controlling of nutrient supply to the nervous tissue, maintenance of extracellular ion balance, and aiding in repair mechanisms of the brain and spinal cord injuries.

Blood brain barrier (BBB): The BBB is a protective network of blood vessels that filters blood flowing to the brain and separates circulating blood and cerebrospinal fluid (CSF) maintained by the choroid plexus in the CNS. Endothelial cells of the blood vessels restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophilic molecules into the CSF, while allowing the diffusion of small hydrophobic molecules (O_2, hormones, CO_2).

Central nervous system (CNS): The CNS is one of the two major divisions of the nervous system and consists of the brain and the spinal cord. The CNS connects to sensory organs (such as the eye and ear) and other organs of the body, muscles, blood vessels, and glands through the peripheral nervous system. The CNS consists of the brain in the cranial cavity and the spinal cord in the spinal cavity.

Hippocampus: The hippocampus is named for its shape like a seahorse (From the Greek *hippos* = horse and *kampos* = a sea monster). It is a closely associated, paired structure with mirror-image halves in the left and right sides of the brain. In humans and other primates, the hippocampus is located inside the medial temporal lobe, beneath the cortical surface. The hippocampus is part of the olfactory cortex essential to the sense of smell and also helps to regulate emotion and memory. Hippocampus also plays important roles in long-term memory and spatial navigation.

Homeostasis: (from Greek: *homoios*, "similar"; and *histēmi*, "standing still"). Generally refers to the property of a system, either open or closed, that regulates its internal environment and tends to maintain a stable, constant condition. When applied to living organisms, homeostasis refers to a property of cells, tissues, and organisms that allow the maintenance and regulation of the stability and constancy needed to function properly and is maintained by the constant adjustment of biochemical and physiological pathways.

Metallothionein (MT): Metallothionein is a family of cysteine-rich, low molecular weight (3.5–14 kDa) proteins. The thiol group of MT contains cysteine residues, which represent ~20–30% of its total amino acidic residues. Both essential (such as Zn, copper, selenium) and toxic (such as cadmium, mercury, silver, arsenic) heavy metals can bind the thiol groups through the cysteine residues. MT has high affinity for Zn (1.4×10^{-13} M). There are four major isoforms (MT-I, MT-II, MT-III, MT-IV) expressed primarily in the liver and kidneys. MT expression is also evident in other tissues and organs such as blood, skin, and heart. In the brain, MT-III is known as the growth inhibitory factor. Expression of MT in different organs and tissues depends on the availability of the dietary minerals, such as Zn, copper, and selenium, and the amino acids histidine and cysteine. MT distributes intracellular Zn as Zn undergoes rapid inter- and intracluster exchange.

Neurogenesis: The process by which new nerve cells are generated i.e., production of new neurons, astrocytes, glia, and other neural lineages from undifferentiated neural progenitor or stem cells. Neurogenesis is most active during prenatal development and inactive in most areas of the adult brain.

Neuron: Neurons are cells in the nervous system including the brain, spinal cord (vertebrate), the ventral nerve cord (invertebrate), and the peripheral nerves that process and transmit information by

electrochemical signaling. A typical neuron has a cell body (soma), branching processes specialized to receive incoming signals (dendrites), and a single process (axon) that carries electrical signals away from the neuron toward other neurons or effectors. Electrical signals carried by axons are action potentials. Different types of neurons are named after their specialized structure and functions: for example, *sensory neurons* respond to touch, sound, light, and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain; *motor neurons* receive signals from the brain and spinal cord and cause muscle contractions and affect glands; *interneurons* connect neurons to other neurons within the same region of the brain or spinal cord.

Dopaminergic neuron: Neurons that produce dopamine, a neurotransmitter produced in several areas of the brain, including the substantia nigra and the ventral tegmental area in either vertebrates or invertebrates. Dopamine is a neurohormone released by the hypothalamus mainly to inhibit the release of prolactin from the anterior lobe of the pituitary.

GABAergic neuron: Neurons that produce γ-aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the mammalian CNS. It plays an important role in regulating neuronal excitability throughout the nervous system. In humans, GABA is directly responsible for the regulation of muscle tone. GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes. This binding causes the opening of ion channels to allow the flow of either Cl^- ions into the cell or K^+ out of the cell. Two general classes of GABA receptor are known: $GABA_A$ in which the receptor is part of a ligand-gated ion channel complex, and $GABA_B$ metabotropic receptors, which are G protein-coupled receptors that open or close ion channels via intermediaries.

Reelin: Reelin is a protein expressed in different tissues of the body including brain, spinal cord, and blood. In the developing brain it helps to regulate neuronal migration and positioning. In the adult brain, it modulates synaptic plasticity by enhancing the induction and maintenance of long-term potentiation. It also stimulates dendrite and dendritic spine development and regulates the continuing migration of neuroblasts generated in adult neurogenesis sites like subventricular and subgranular zones.

Subventricular zone (SVZ): The subventricular zone is a paired brain structure situated throughout the lateral walls of the lateral ventricles. Along with the subgranular zone of the dentate gyrus, the SVZ serves as a source of neural stem cells in the process of neurogenesis. It harbors the largest population of proliferating cells in the adult brain of rodents, monkeys, and humans.

Synaptic vesicle: Synaptic vesicles or neurotransmitter vesicles are 40–100 nanometers in diameter, and made up of a lipid bilayer, store various neurotransmitters (NT) that are released at the synapse for synaptic transmission. The release of NTs is regulated by a voltage-dependent Ca^+ channel. At synapses, the junctional complexes between presynaptic membranes (synaptic knobs) and postsynaptic membranes (receptor surfaces of recipient neurons or effectors), synaptic transmission process signal transfer (communicate) from one neuron (affector) to other neurons (effectors).

Zinc finger transcription factor: Zinc finger transcription factors are the DNA-binding proteins, containing Zn finger domain. Zinc fingers are small protein domains, folds of which are stabilized by one or more Zn^{2+}. They coordinate Zn^{2+} with a combination of cysteine and histidine residues. Different families of Zn finger proteins can bind DNA, RNA, proteins or small molecules involved in transcription, nucleic acid polymerization, and histones.

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