ZINC IN THE ANIMAL ORGANISM: A REVIEW*

V. Sloup, I. Jankovská, S. Nechybová, P. Peřinková, I. Langrová

Czech University of Life Sciences Prague, Faculty of Agrobiology, Food and Natural Resources, Prague, Czech Republic

Zinc, as an essential metal, is necessary for the correct function of an organism. It is involved in biochemical processes that affect the immune response of an organism, and it acts as a neuromodulator in the excitatory synapses of the brain. Zinc is also applied in response to stressful stimuli. Zinc is an essential factor of gene expression and is important, at the cellular level, in maintaining the integrity of the cell walls. It influences organism ageing. Zinc is relatively abundant in nature, and it exists in a mineral form and rarely as a pure element. Zinc is used widely in industry and agriculture. In industry, it is utilized mainly in the processing of other metals as protection against corrosion. In agriculture, it is used in fertilizers and chemicals to produce pesticides. In certain areas affected by human activities, its concentrations increase, and large quantities of this metal can get into the food supply. In this paper, we focus on zinc metabolism and homeostasis, with an emphasis placed on the biological function of zinc. This study also deals with zinc deficiency and its effect on health. We also touch on the excessive intake of zinc and its toxicity.

metal, enzyme, protein, metallothionein

DE GRUYTER OPEN

doi: 10.1515/sab-2017-0003
Received for publication on October 16, 2015
Accepted for publication on July 7, 2016

INTRODUCTION

Zinc (Zn) is one of the most important nutrients for animal health. Numerous proteins, crucial enzymes, and transcription factors bind to Zn and are thought to be dependent on Zn for their functions. Zn is involved in many biochemical processes that support life. The most important of these are cellular respiration, cellular use of oxygen, DNA and RNA expression, maintenance of cell membrane integrity, sequestration of free radicals, and protection against lipid peroxidation. Zn is a trace element that is a central component of metalloenzymes, lactate dehydrogenase, carboxypeptidase, and DNA and RNA polymerases. The human body contains 1.5–2.5 g of Zn, with 60% found in muscle and 30% in bones (Fig. 1). The recommended dose of zinc is 11 mg/day for adult men and 8 mg/day for adult women (Cousins, 1998; Brown et al., 2001; Erdman et al., 2012 – see Table 1).

Zn is an essential metal involved in many biochemical processes, and it is associated with a wide range of physiological defects, including disorders of the skin, anorexia, weight loss, growth retardation, and impaired neurologic and immune systems. Zn deficiency in children depresses growth, appetite, skeletal maturation, and gonad development, which can be reversed with Zn treatment. Zn deficiency also causes alterations in the activities of some enzymes such as ALP, copper/Zn superoxide dismutase (Cu-Zn SOD), carboxypeptidases, DNA and RNA polymerases, and lactate dehydrogenase (Cuajungco, Lees, 1997; Brody 1998; Frederickson et al. 2005; Sun et al., 2011).

Zn is involved in the maintenance of gut structure and function, and plays a vital role in gut immune function. Zn deficiency causes villi of the jejunum to become shrivelled and flattened. This change in morphology decreases surface area absorption, and there

* Supported by the Internal Grant Agency of the Czech University of Life Sciences Prague (CIGA), Project No. 20152021, and by the Czech Science Foundation (GACR), Project No. 13-18154S.

was a substantial decrease in the number of villi per unit area. Zn supplementation leads to an accelerated regeneration of the mucosa and to increased levels of brush border enzymes (Sun et al., 2011).

Nutritional Zn deficiency is a worldwide problem (Fig. 2). The risk of inadequate Zn intake through diet is greatest in Africa, the Middle East, and South America. Insufficient intake of Zn is associated with protein-energy malnutrition (Wessells, Brown, 2012). Zn deficiency is associated with metabolic disturbances in a wide range of hormones, cytokines, and enzymes involved in growth and bone development (e.g. insulin-like growing factor-I (IGF-1), growth hormone, thyroid hormone, insulin, prolactin, alkaline phosphatase (ALP), and prostaglandins). Inadequate Zn intake in both humans and animals has been shown to cause growth retardation and delayed skeletal maturation. ALP, a Zn-metalloenzyme found on the surface of osteoblasts, is essential for normal bone formation and/or mineralization. Bone-specific ALP contains two Zn molecules per enzyme monomer, and this enzyme-bound Zn is required for ALP activity. Moreover, removal of Zn by chelation results in an irreversible loss of bone-specific ALP activity. Previous animal studies indicated that bone-specific ALP activity decreased in the bones of Zn-deficient rats. In addition, there is a dose-dependent relationship between dietary Zn and skeletal ALP in the tibia of adult female mice. Carbonic anhydrase II (CAII), a Zn-containing enzyme that catalyzes the reversible hydration of carbon dioxide, is an initial regulator of osteoblast differentiation, and is essential in optimal bone resorption (Kukačka et al., 2008; Sun et al., 2011).

Proteins for Zn transport, zinc finger proteins, and metallothioneins (MTs) are all non-enzymatic zinc proteins. Two protein families have been implicated in Zn transport: ZnT proteins and Zip proteins. Dysregulation in Zn transport via specific protein transporters has been linked to specific diseases. MTs, a superfamily of non-enzymatic peptides with low molecular mass and a unique sequence of amino acids, play a significant biological role in immunoregulation, neuroprotection, metalloregulation, and detoxification (Ladomery, Dellaire, 2002; Kukačka et al., 2008).

An overdose of Zn is not possible through a normal diet. In the cases where nutritional supplements enriched by Zn are taken in high doses, the metabolism of other metals may be disturbed; dietary Zn has anantagonistic effect on Cu absorption. Animals given low amounts of Zn retained more Cu than did animals fed high levels of Zn (Fisher et al., 1981). When Zn is taken in extremely high doses, it is absorbed in the intestines at the expense of other metal ions, and the amount of Cu, Fe, Co or Cr decreases. If this continues unchanged, symptoms of anaemia can arise. This means we must ensure a balanced intake of all biogenic metals in order to prevent any distortion of stability during penetration of the intestinal wall (Ferguson et al., 1995; Brody, 1998; Brown et al., 2001).

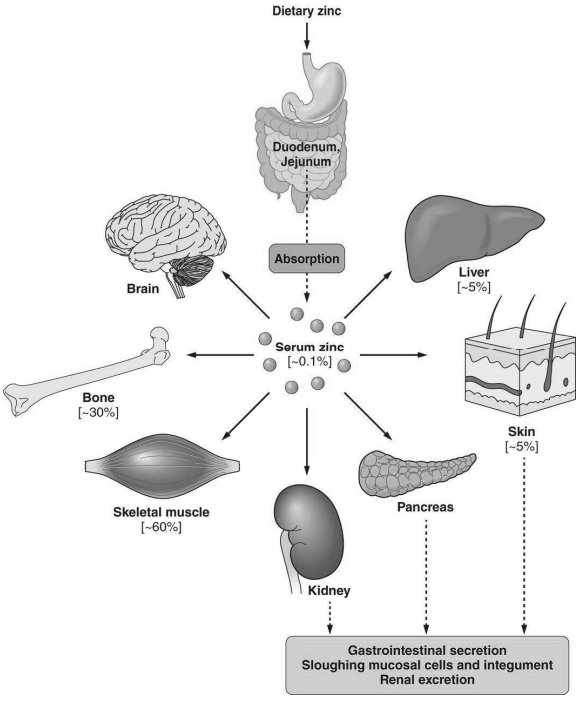

Fig 1. The distribution of zinc in various tissues (Kambe et al., 2015)

Zinc contamination of agroecosystems

Zinc, like other trace elements (Cu, Mn, Co, Ni), enters an agroecosystem in two ways. The first way is during the weathering of parent material that contains high concentrations of minerals containing Zn. The three main minerals that contain Zn are smithsonite ($ZnCO_3$), sphalerite (ZnS), and hemimorphite ($Zn_4Si_2O_7(OH)_2 \cdot H_2O$). Basalts, for example, are igneous rocks with high levels of Zn. Sedimentary rocks with high levels of Zn are known as slates (Zhenli et al., 2005). These minerals may rapidly weather under the influence of specific environmental conditions. Trace elements in them are oxidized and thus become mobile (Shuman, 1991; Zhenli et al., 2005).

The second method of entry is through anthropogenic activity. Anthropogenic processes include the application of fertilizers, fungicides, herbicides, pesticides, and pond sediments on agricultural land, which contains levels of various trace elements including Zn. For example, the application of agricultural chemicals in orchards may increase Zn content by 5–9 kg/ha of land per year (Shuman, 1991; Zhenli et al., 2005). Zn also enters agro-ecosystems via animal excreta. Zn is an inorganic antimicrobial compound, and in order to prevent excessive Zn in agricultural

Table 1. The recommended daily intake of zinc by age and sex (Erdman et al., 2012)

Life stage	Age	AI (mg/day)		EAR (mg/day)		RDA (mg/day)		UL (mg/day)	
		Male	Female	Male	Female	Male	Female	Male	Female
Infants	0-6 months	2.0	2.0					4.0	4.0
	7-12 months			2.5	2.5	3.0	3.0	5.0	5.0
Children	1-3 years			2.5	2.5	3.0	3.0	7.0	7.0
	4-8 years			4.0	4.0	5.0	5.0	12.0	12.0
	9-13 years			7.0	7.0	8.0	8.0	23.0	23.0
	14-18 years			8.5	7.3	11.0	9.0	34.0	34.0
Adults	> 19 years			9.4	6.8	11.0	8.0	40.0	40.0
Pregnancy	14-18 years				10.0		12.0		34.0
	19-50 years				9.5		11.0		40.0
Lactation	14-18 years				10.9		13.0		34.0
	19-50 years				10.4		12.0		40.0

AI, adequate intake; EAR, estimated average requirement; RDA, recommended dietary allowance; UL, tolerable upper intake level.

land, EU legislation has limited Zn content in complete feed mixtures to 250 mg/kg or 80 mg/kg in chelated Zn (Comission Regulation (EC) No. 2316/98). Only small portions of trace elements in soil are bioavailable. Trace element mobility and accessibility are affected by many chemicals and biochemical processes such as dissolving in rainwater, adsorption–desorption, complexation reactions, dissociation, and oxidation-reduction reactions. Zn mobility is affected by soil pH as well as various biological processes (Zhenli et al., 2005).

Heavy metal pollution is a consequence of human activity that affects all components of an ecosystem, mainly the soil. Many authors have analyzed how plants respond to this pollution and plant ability to accumulate metal in different tissues (Berchová-Bímová et al., 2014; Břendová et al., 2015; Száková et al., 2016; Tlustoš et al., 2016).

Zinc metabolism

Food is the main source of Zn. Relatively high concentrations of this element are found in meat (especially beef and pork, but also turkey and chicken), seafood (oysters are considered a great Zn source), cereals, and legumes. Generally, animal-based foods are a more preferable source of Zn than plant-based foods. Animal-based foods contain hardly any compounds that inhibit Zn absorption. Especially zero phytate content is the important thing. Phytic acid reduces bioavailability of Zn by forming insoluble complexes together. The presence of certain amino

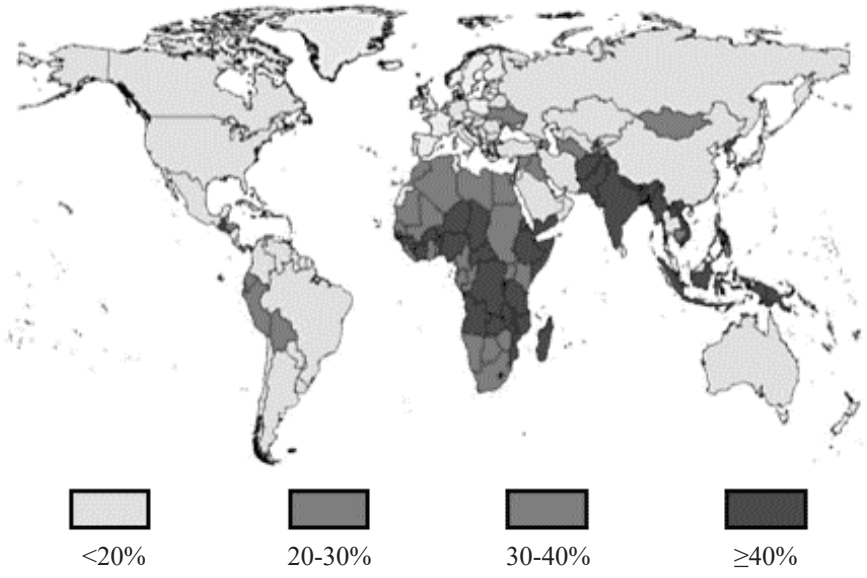

Fig. 2. Estimate of inadequate intake of zinc from food in individual countries (Wessels, Brown, 2012)

acids improves absorption of Zn, cysteine, and histidine (Brown et al., 2001).

Zinc absorption

The main site of Zn absorption in animals is the small intestine, where the distal duodenum and proximal jejunum play a key role. Zn absorption takes place by two means: active and passive transport. Active transport is carried out by specific transporters, and its effectiveness increases with increasing dietary Zn intake. Passive transport operates on a diffusion mechanism, and its effectiveness is proportional to the concentration of Zn in the intestinal lumen (Cousins, 1998; Krebs, 2000).

Zn absorption at the cellular level is a process of entry into the enterocyte and Zn through the basolateral membrane transports into the portal circulation. This process is carried out using several proteins known as zinc transporters (Cousins, 1998; Krebs, 2000).

Zinc distribution

Absorbed Zn is transported in the plasma bound mostly to albumin (60–80%), less on a-2-macroglobulin and transferrin, but also bound to free amino acids, especially histidine and cysteine. Zn bound to plasma proteins is the most freely available and easily available supply of Zn in the body, although it represents only about 0.1% of the total amount of Zn in the body. Blood contains five times more Zn than plasma. In erythrocytes, 80% of Zn is contained in carbonic anhydrase and Zn-superoxide dismutase (Cousins et al., 2006).

Zn transported to the liver is later released into the body. In hepatocytes, enterocytes, and other cells, Zn is kept in custody on metalloproteins. Metalloproteins include metalloenzymes, gene regulation molecules, storage proteins, and zinc transporters. Zn in hepatocytes is primarily bound to MTs (Cousins et al., 2006).

Zinc transporters

Zinc transporters are divided into two groups: ZnT and ZIP. Forwarders group ZnT exports Zn out of the cytoplasm. ZnTs are found mainly on the cytoplasmic membrane, Golgi, endosome, and the endoplasmic reticulum. This group includes ZnT-1, which is located on the plasma membrane. This protein transports Zn from the cell into the extracellular space in almost all tissues. Furthermore, ZnT-2 also transports Zn out of the cell, but it also has the ability to transport Zn into storage vesicles in the cell (under conditions of high concentrations of Zn in the cell). This function is carried out mainly in the acinar cells of the pancreas. Furthermore, it is located in the intestine, kidneys, and testes. The ZnT-3 activity is associated with the transfer of Zn to vesicles, and its expression is restricted to the brain. This demonstrates the important role of Zn in the central nervous system. ZnT-4 is located in the mammalian glands and brain. ZnT-5 is localized on the vesicles secretory cells of the pancreas and the apical membrane of the enterocytes (apical part of the plasma membrane is for absorption; this area is called brush border). ZnT-10 is localized on the cytoplasmic membrane (Robinson et al., 2001; Coyle et al., 2002; Huang et al., 2005; Cousins et al., 2006; Kukačka et al., 2008).

The ZIP group of carriers can be divided into four subgroups: Zip I, Zip II, gufA, and LZT. Most proteins of ZIP group (Zip 4–8, Zip 10, and Zip 12–14) belong to subgroup LZT. Zip 1–3 belong to subgroup ZIP II, Zip 9 belongs to subgroup ZIP I, and protein Zip 11 is a member of subgroup gufA. The zinc transporter Zip 6 of LZT subgroup was subsequently included in a separate subgroup labelled LIV-1 (Robinson et al., 2001; Coyle et al., 2002; Cousins et al., 2006; Kukačka et al., 2008).

It was found that ZIP zinc is transferred into the cells cytoplasm from the extracellular space or intracellular vesicles. Most of them are located on the cytoplasmic membrane. However, Zip 7 is located in the Golgi. ZIP 14 is mobilized to the membrane in the hepatocytes in the case of acute inflammation, thereby increasing Zn absorption (Robinson et al., 2001; Coyle et al., 2002; Kukačka et al., 2008).

Metallothionein

Metallothioneins (MTs) are a group of intracellular proteins with low molecular weight. MT can bind to divalent metal cations, including Zn. MT is composed of 60–68 amino acids, twenty of which are cysteines. The human genome contains at least 16 genes for MT. These genes encode proteins with closely related sequences, and are expressed in different tissue types – mainly in the liver, kidneys, intestine, pancreas, and brain (Robinson et al., 2001; Coyle et al., 2002). All MTs are characterized not only by a high content of cysteine, but also by the binding of metal ions by thiolates and the creation of cysteinyl–thiolate clusters with a characteristic spatial arrangement (Alberts et al., 1998; Miles et al., 2000; Adam et al., 2008).

MT performs many functions in the body, the most important being the transport of essential metal ions and detoxification of toxic levels of metal ions. Most of MTs bind zinc. MTs act also as a reservoir of excess metal ions. They can be mobilized during conditions of insufficient metal ion intake (Robinson et al., 2001; Coyle et al., 2002).

The mammalian MT contains 61 to 68 amino acid residues, in which 18 to 23 cysteine residues are present. None is an aromatic amino acid or histidine. The chain of amino acids is as follows: Cys-Cys, Cys-X-Cys, and Cys-X-X-Cys (X represents an amino acid differ-

ent from cysteine). This is characteristic of MT. The tertiary structure of MTs is composed of two domains (α: stable domain containing the C-terminal end, and β: reactive domain containing the N-terminal end). They coordinate 7 divalent or 12 monovalent metal ions. In organisms, MT occurs in several isoforms: MT-1, MT-2, MT-3, and MT-4 (Quaife et al., 1994; Miles et al., 2000; Vašák, Hasler, 2000; Mejáre, Bűlow, 2001; Coyle et al., 2002).

Regulation of the MT expression is associated with the presence of metal ions. Transcription is initiated after the establishment of metal-regulatory transcription factor-1 (MTF-1) to the metal responsive element (MRE), which lies on the MT gene promoter. Normally, the MTF-1 are bound to MTI, an inhibitor that prevents binding MTF-1 MRE. After entering the metal ion into the intracellular compartment cell creates links between the ion and MTI. Thus the MTF-1 is released and induces the expression of MT (Masters et al., 1994; Adam et al., 2008).

Zinc excretion

Following oral exposure, Zn is primarily excreted via the gastrointestinal tract and eliminated in the faeces; approximately 70–80% of an ingested dose is excreted (Davies, Nightingale, 1975). Pancreatic zinc secretion at homeostasis is 2-4 times the size of the dietary contribution into the duodenum (Oberleas, 1996); most of this secreted zinc is later reabsorbed. It depends primarily on the Zn content in the diet. The amount of Zn found in compound feed for livestock is around 100 mg/kg. Stools contain unabsorbed Zn from food, Zn contained in released intestinal epithelial cells, and endogenous Zn secreted into the intestine from the pancreas and gallbladder (Koyama et al., 1993; Krebs, 2000).

Endogenous intestinal losses can range from 0.5 to 3 mg/day, depending on Zn intake. In normal healthy subjects approximately 0.7 mg Zn per day is lost through urine. Starvation and muscle catabolism increase Zn losses in urine and faeces. The loss of Zn in perspiration and desquamated epidermal cells has been estimated at 0.5 mg/day in adult men; however, this depends on Zn intake (Krebs, 2000).

In humans, approximately 14% of eliminated Zn is excreted in urine; when Zn intake increases, urinary excretion accounts for 25% of eliminated Zn (Wastney et al., 1986). Other minor routes of elimination include sweat (Prasad et al., 1963), saliva secretion (Greger, Sickles, 1979), and incorporation into hair (Rivlin, 1983).

The rate, at which Zn is excreted, is dependent on both current and past Zn intake (Johnson et al., 1988). Age also affects the rate at which Zn is excreted. He et al. (1991) reported that following an intraperitoneal dose of Zn, adult mice had higher levels of Zn in faecal excretions than weanling, adolescent, or young adult mice.

Zinc supplementation in farm animal diets

The reproductive well-being and performance of farm animals is largely dependent on their nutritional status. Micronutrients are especially involved in functions such as intracellular detoxification of free radicals, synthesis of reproductive steroids and other hormones, carbohydrate, protein, and nucleic acid metabolism. Their deficiency and/or excess may impair spermatogenesis and libido in male, fertility, embryonic development and survival, postpartum recovery activities, milk production, and offspring development and survival (Smith, Akinbamijo, 2000). In animals, Zn deficiency can also be manifested through changes in taste perception (accompanied by the tongue epithelium damage), a disorder of keratin synthesis, limited limb bone growth, and sight disorders (Hosnedlová et al., 2007). The mechanism of growth retardation in the case of Zn deficiency can be seen in loss of appetite, imperfect use of nutrients from feedstuffs, and in disorders of the protein and energy metabolism (Illek et al., 2000). One specific disorder resulting from Zn deficiency is parakeratosis – a disorder of the epidermal layer of the skin that occurs in calves, sheep, goats, and piglets. In calves, it is manifested by a characteristic coat shedding that occurs on the head, neck, limbs, and around the eyes ('glasses') (Suchý et al., 1998). Similar findings were observed in free living ruminants by Abdou (2005). Ali et al. (1998) compared two groups of mature ewes that were fed either a control diet containing 23–25 ppm Zn or a test diet supplemented with additional 100 ppm in form of zinc sulphate. Supplementation began one month before mating and continued until lambing period. The above mentioned authors reported that ewes given Zn supplements consumed by about 15% more feed than the controls, had a higher fertility rate, were more prolific (89 vs 40%), and produced heavier lambs at birth (4.0 vs 2.9 kg) and at weaning (17.7 vs14.2 kg).

It has been known for some time that feeding high concentrations of Zn, Fe and/or Ca to animals reduces the rate of absorption of Cd from various food sources. When Zn was marginal in the diet, the delay of Cd excretion was more pronounced (Reeves, Chaney, 2004). The rates of dietary Cd absorption and whole-body retention increased 7–10 fold when experimental animals were fed diets containing marginal concentrations of Zn, Fe and/or Ca (Reeves, Chaney, 2001, 2002).

Excess Zn intake is a relatively rare occurrence in farm animals. It transpires, for example, in piglets treated with medications high in Zn. Excess Zn reduces the digestibility of phosphorus, and causes anaemia and digestive disorders. Poisoning is conditioned

primarily by the antagonistic relationship of Zn to Fe and Cu (Suchý et al., 1998). Noakes et al. (2001) note that excess intake of Zn additives may lead to a disorder of essential fatty acid metabolism, which influences prostaglandin synthesis.

Matrix metalloproteinase

Matrix metalloproteinases (MMPs) are a large group of Zn-dependent proteins that are responsible for cleavage and the adjustment of individual components of connective tissue such as collagen, elastin, gelatin, and casein. Degradation of connective tissue with intensive participation of MMP is a process that takes place during ontogenetic changes in the organism such as growth, morphogenesis, as well as wound healing and tissue damage. It also includes MMP activity in diseases and pathological processes closely related with tissues, e.g. inflammation, tumours, and skin diseases. Most of these enzymes (excluding membrane MMPs) are secreted from the cells in the form of a proenzyme which is activated as needed by Zn ions for actual cleavage rate. Among other things, in the MMP molecule there are Ca ions with structural function. MMPs are homologous proteins, which can be divided into six categories: collagenase, stromelysin, matrilysin, gelatinase, membrane metalloproteinase, and other MMPs. MMPs are Zn- and Ca-dependent endopeptidases, and they are synthesized as inactive preproenzymes (zymogens). This inactive form prevents MMPs from cleaving to the essential components of the cell. MMPs are mostly secreted from cells as inactive proenzymes, except the membrane-bound MMPs (Vanwart, Birkedalhansen, 1990; Masters et al., 1994; Aimes, Quigley, 1995).

Extracellular enzyme activation involves two steps: the first is the initial cleavage of the propeptides of MMP by the protease and destabilization of the propeptide binding interactions. The second is cleavage of the propeptides by other MMPs (Nagase et al., 1991; Aimes, Quigley, 1995; Anand-Apte et al., 1996; Ogata et al., 2001).

Transcriptional function of zinc

There are more than 2000 transcription factors or DNA binding proteins that are dependent on zinc. They are involved in the gene expression of various proteins. These are regulatory proteins that bind to the promoter region in the DNA and allow the initiation of transcription (i.e. the transcription of DNA into RNA). Transcriptional factors binding to DNA have specific structural motifs (the amino acid sequences) to enable this relationship. One of the most important structural motifs is the so-called 'zinc finger'(Ladomery, Dellaire, 2002; Sun et al., 2006).

'Zinc fingers' are protein domains that occur in many different transcription factors, and they allow a (transcription) factor to bind to a specific DNA sequence. The name is inspired by their shape, which consists of a sequence of roughly 30 amino acids strongly bound to the Zn atom. This amino acid sequence contains, among other things, two histidine and two cysteine residues. They are coordinated to one Zn atom. Therefore, 'zinc fingers' usually refer to Cys2His2. The Zn atom is required to bind protein to DNA. Perhaps the most well-known member of this group is the commonly occurring factor Sp1, whose DNA binding domain is composed of three zinc fingers (Ladomery, Dellaire, 2002; Sun et al., 2006).

Proteins that comprise zinc fingers are important in transcription, translation, cytoskeleton organization, developing epithelial cell adhesion, chromatin remodelling proteins, and the arrangement of tertiary structures (Cousins, 1998; Sun et al., 2006).

Another group in which Zn plays an important role in DNA binding are the steroid hormone receptors. These receptors are located in the cytoplasm or nucleus.

Synthesis of insulin

Zinc is indispensable for the synthesis and effectivity of the insulin hormone. Insulin is stored in b-cells of pancreatic islets (in secretory vesicles of Langerhans islets). Into the bloodstream it is carried continuously and its level increases with increasing levels of blood glucose (Prasad, 1998).

Insulin hormones are arranged in a regular crystalline structure comprising Zn ions in secretory vesicles. Each insulin molecule is linked with 2–4 Zn atoms. A zinc/insulin complex is formed for the purpose of slow release of insulin into the bloodstream (Prasad, 1998).

CONCLUSION

Zinc is indispensable for correct growth and development of an organism. It is involved in DNA replication and RNA transcription. In addition to its role in the transcription and translation of genetic material, Zn has an important function in the primary endocrine system, which is involved in growth hormone metabolism of somatotropin. Zinc is associated with reduced concentrations of circulating growth factor, which is similar to insulin-like growth factor 1 (IGF-1), and it is necessary for the correct function of somatotropin. Experiments on animals have shown that Zn deficiency leads to a decrease in food intake, in comparison with control animals administered the correct amount of Zn in feed. In a population that experienced growth retardation, growth was renewed and body weight increased following Zn supplementation

Zinc is extremely important for the immune system. When Zn is deficient, thymic atrophy occurs and thymulin activity is reduced. Thymulin is a hor-

mone that requires Zn in order to become active. Thymulin hormone is responsible for the maturation of T-lymphocytes, cytotoxicity, and cytokine production. Moreover, the development of B-lymphocytes and production of antibodies (especially immunoglobulin G (IgG)) are disturbed. The role of Zn in these immunological processes derives from its involvement in basic cellular functions such as DNA replication, RNA transcription, cell division, and cell activation.

Zinc is also an important antioxidant factor. It is involved in protecting biological structures from free radical damage by maintaining sufficient levels of MT. Zn is an essential component of the enzyme superoxide dismutase (SOD), protects thiol groups (-SH) from oxidation, prevents interaction between the thiol groups, helps prevent lipid peroxidation in mitochondria and microsomal membranes, stabilizes the structure of cell membranes, and prevents damage to the osmotic membranes of erythrocytes. The *p53* tumour suppressor gene (the most frequently mutated gene in human cancer patients) is a transcription factor that contains Zn, and its expression is dependent on this element. This has shown to be an extremely significant finding.

Programmed cell death, or apoptosis, is a regulated biological mechanism that is vital for the health of the immune system. It has been found that Zn plays an important role in the regulation of apoptosis. Zn has the ability to block apoptosis that is induced by external factors.

Acknowledgement

The authors gratefully acknowledge Brian Kavalir (Toronto, Canada) for his proofreading services.

REFERENCES

Abdou TA (2005): Parakeratosis in Egyptian buffaloes. Livestock Production Science, 98, 175–194.

Adam V, Blaštík O, Křížková S, Lubal P, Kukačka J, Průša R, Kizek R (2008): Application of the Brdicka reaction in determination of metallothionein in patients with tumours. Chemické Listy, 102, 51–58.

Aimes RT, Quigley JP (1995): Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. The Journal of Biological Chemistry, 270, 5872–5876.

Alberts IL, Nadassy K, Wodak SJ (1998): Analysis of zinc binding sites in protein crystal structures. Protein Science, 7, 1700–1716. doi: 10.1002/pro.5560070805.

Ali HA, Ezzo OH, El-Ekhnawy KE (1998): Effect of zinc supplementation on reproductive performance of Barki ewes under practical field condition. Veterinary Medical Journal Giza, 46, 77–87.

Anand-Apte B, Bao L, Smith R, Iwata K, Olsen BR, Zetter B, Apte SS (1996): A review of tissue inhibitor of metalloproteinases-3 (TIMP-3) and experimental analysis of its effect on primary tumor growth. Biochemistry and Cell Biology, 74, 853–862. doi: 10.1139/096-090.

Berchová-Bímová K, Soltysiak J, Vach M (2014): Role of different taxa and cytotypes in heavy metals absorption in knotweeds (Fallopia). Scientia Agriculturae Bohemica, 45, 11–18. doi: 10.7160/sab.2014.450102.

Břendová K, Tlustoš P, Száková J (2015): Biochar immobilizes cadmium and zinc and improves phytoextraction potential of willow plants on extremely contaminated soil. Plant, Soil and Environment, 61, 303–308.

Brody T (1998): Zinc and copper. Nutritional Biochemistry. Academic Press, San Diego.

Brown KH, Wuehler SE, Peerson JM (2001): The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency. Food and Nutrition Bulletin, 22, 113–125. doi: 10.1177/156482650102200201.

Cousins RB, Liuzzi JP, Lichten LA (2006): Mammalian zinc transport, trafficking and signals. The Journal of Biological Chemistry, 281, 24085–24089. doi: 10.1074/jbc.R600011200.

Cousins RJ (1998): Role of zinc in the regulation of gene expression. Proceedings of the Nutrition Society, 57, 307–311. doi: 10.1079/PNS19980045.

Coyle P, Philcox JC, Carey LC, Rofe AM (2002): Metallothionein: the multipurpose protein. Cellular and Molecular Life Sciences, 59, 627–647. doi: 10.1007/s00018-002-8454-2.

Cuajungco MP, Lees GJ (1997): Zinc metabolism in the brain: relevance to human neurodegenerative disorders. Neurobiology of Disease, 4, 137–169. doi: 10.1006/nbdi.1997.0163.

Davies NT, Nightingale R (1975): The effect of phytate on intestinal absorption and secretion of zinc and whole body retention of Zn, copper, iron and manganese in rats. British Journal of Nutrition, 34, 243–258.

Erdman Jr. JW, Macdonald IA, Steven HZ (2012): Present knowledge in nutrition. Wiley-Blackwell Publishing, Hong Kong.

Ferguson LE, Gibson SR, Opare-Obisaw C, Ounpuu S, Lamba CH (1995): Dietary strategies for improving the zinc nutriture of rural, southern Malawian and Ghanaian children. Ecology of Food and Nutrition, 34, 33–47. doi: 10.1080/03670244.1995.9991445.

Fischer PW, Giroux A, L'Abbé MR (1981): The effect of dietary zinc on intestinal copper absorption. The American Journal of Clinical Nutrition, 34, 1670–1675.

Frederickson CJ, Koh J-Y, Bush AI (2005): The neurobiology of zinc in health and disease. Neuroscience, 6, 449–462. doi: 10.1038/nrn1671.

Greger JL, Sickles VS (1979): Saliva zinc levels: potential indicators of zinc status. American Journal of Clinical Nutrition, 32, 1859–1866.

He LS, Yan XS, Wu DC (1991): Age-dependent variation of zinc-65 metabolism in LACA mice. International Journal of Radiation Biology, 60, 907–916.

Hosnedlová B, Trávníček J, **Šoch** M (2007): Current view of the significance of zinc for ruminants: a review. Agricultura Tropica et Subtropica, 40, 57–64.

Huang L, Kirschke CP, Zhang Y, Yu YY (2005): The *ZIP7* gene (*Slc39a7*) encodes a zinc transporter involved in zinc homeostasis of the Golgi apparatus. Journal of Biological Chemistry, 280, 15456–15463. doi: 10.1074/jbc.M412188200.

Illek J, Bečvář O, Lokajová E, Matějíček M (2000): Trace elements in nutrition of cattle – zinc. Krmivářství, 6, 30. (in Czech)

Johnson PE; Hunt JR; Ralston NV (1988): The effect of past and current dietary Zn intake on Zn absorption and endogenous excretion in the rat. The Journal of Nutrition, 118, 1205–1209.

Kambe T, Tsuji T, Hashimoto A, Itsumura N (2015): The physiological, biochemical, and molecular roles of zinc transporters in zinc homeostasis and metabolism. Physiological Reviews, 95, 749–784. doi: 10.1152/physrev.00035.2014.

Koyama H, Satoh H, Rivai IF, Suzuki S (1993): High zinc content of scalp hair in rural West Java: a rice-eating community. Ecology of Food and Nutrition, 30, 275–282. doi: 10.1080/03670244.1993.9991341.

Krebs NF (2000): Overview of zinc absorption and excretion in the human gastrointestinal tract. The Journal of Nutrition, 130, 1374–1377.

Kukačka J, Kizek R, Průša R (2008): Future of zinc metalloproteins in laboratoty medicine. Klinická biochemie a metabolismus, 16, 161–170. (in Czech)

Ladomery M, Dellaire G (2002): Multifunctional zinc finger proteins in development and disease. Annals of Human Genetics, 66, 331–342. doi: 10.1017/S0003480002001215.

Masters BA, Quaife CJ, Erickson JC, Kelly EJ, Froelick GJ, Zambrowicz BP, Brinster RL, Palmiter RD (1994): Metallothionein III is expressed in neurons that sequester zinc in synaptic vesicles. Journal of Neuroscience, 14, 5844–5857.

Mejáre M, Bülow L (2001): Metal-binding proteins and peptides in bioremediation and phytoremediation of heavy metals. Trends in Biotechnology, 19, 67–73. doi: 10.1016/S0167-7799(00)01534-1.

Miles AT, Hawksworth GM, Beattie JH, Rodilla V (2000): Induction, regulation, degradation and biological significance of mammalian metallothioneins. Critical Reviews in Biochemistry and Molecular Biology, 35, 35–70. doi: 10.1080/10409230091169168.

Nagase H, Suzuki K, Enghild JJ, Salvesen G (1991): Stepwise activation mechanisms of the precursors of matrix metalloproteinases-1 (tissue collagenase) and 3 (stromelysin). Biomedica Biochimica Acta, 50, 749–754.

Noakes DE, Parkinson TJ, England GCW, Arthur GH (2001): Arthur's Veterinary Reproduction and Obstetrics. W.B. Saunders, Philadelphia.

Oberleas D (1996): Mechanism of zinc homeostasis. Journal of Inorganic Biochemistry, 62, 231–241.

Ogata Y, Miura K, Ohkita A, Nagase H, Shirouzu K (2001): Imbalance between matrix metalloproteinase 9 and tissue inhibitor of metalloproteinases 1 expression by tumor cells implicated in liver metastasis from colorectal carcinoma. The Kurume Medical Journal, 48, 211–218.

Prasad AS (1998): Zinc deficiency in humans: a neglected problem. Journal of the American College of Nutrition, 17, 542–543. doi: 10.1080/07315724.1998.10718800.

Prasad AS, Schulert AR, Sandstead HH (1963): Zinc, iron, and nitrogen content of sweat in normal and deficient subjects. Journal of Laboratory and Clinical Medicine, 62, 84–89.

Quaife CJ, Findley SD, Erickson JC, Froelick GJ, Kelly EJ, Zambrowicz BP, Palmiter RD (1994): Induction of a new metallothionein isoform (mt-iv) occurs during differentiation of stratified squamous epithelia. Biochemistry, 33, 7250–7259. doi: 10.1021/bi00189a029.

Reeves PG, Chaney RL (2001): Mineral status of female rats affects the absorption and organ distribution of dietary cadmium derived from edible sunflower kernels (*Helianthus annuus* L.). Environmental Research, 85, 215–225.

Reeves PG, Chaney RL (2002): Nutritional status affects the absorption and whole-body and organ retention of cadmium in rats fed rice-based diets. Environmental Science and Technology, 36, 2684–2692.

Reeves PG, Chaney RL (2004): Marginal nutritional status of zinc, iron, and calcium increases cadmium retention in the duodenum and other organs of rats fed rice-based diets. Environmental Research, 96, 311–322.

Rivlin RS (1983): Misuse of hair analysis for nutritional assessment. The American Journal of the Medical Sciences, 75, 489–493.

Robinson NJ, Whitehall SK, Cavet JS (2001): Microbial metallothioneins. Advances in Microbial Physiology, 44, 183–213. doi: 10.1016/S0065-2911(01)44014-8.

Shuman LM (1991): Chemical forms of micronutrients in soils. In: Mortvedt JJ, Cox FR, Shuman LM, Welch RM (eds): Micronutrients in agriculture. Soil Science Society of America, Madison.

Smith OB, Akinbamijo OO (2000): Micronutrients and reproduction in farm animals. Animal Reproduction Science, 60–61, 549–560.

Suchý P, Suchý Jr. P, Straková E (1998): Microelements in nutrition of farm animals. Krmiva & Výživa, 3–4, 18–19. (in Czech)

Sun JY, Jing MY, Wang JF, Zi NT, Fu LJ, Lu MQ, Pan L (2006): Effect of zinc on biochemical parameters and changes in related gene expression assessed by cDNA microarrays in pituitary of growing rats. Nutrition, 22, 187–196. doi: 10.1016/j.nut.2005.07.007.

Sun JY, Wang JF, Zi NT, Jing MY, Weng XY (2011): Effects of zinc supplementation and deficiency on bone metabolism and related gene expression in rat. Biological Trace Element Research, 143, 394–402. doi: 10.1007/s12011-010-8869-9.

Száková J, Krýchová M, Tlustoš P (2016): The risk element contamination level in soil and vegetation at the former deposit of galvanic sludges. Journal of Soils and Sediments, 16, 924–938. doi: 10.1007/s11368-015-1301-5.

Tlustoš P, Břendová K, Száková J, Najmanová J, Koubová K (2016): The long-term variation of Cd and Zn hyperaccumulation by Noccaea spp. and Arabidopsis halleri plants in both pot and field conditions. International Journal of Phytoremediation, 18, 110–115. doi: 10.1080/15226514.2014.981243.

Vanwart HE, Birkedalhansen H (1990): The cysteine switch – a principle of regulation of metalloproteinase activity with potential applicability to the entire matrix metalloproteinase gene family. Proceedings of the National Academy of Sciences of the United States of America, 87, 5578–5582.

Vašák M, Hasler DW (2000): Metallothioneins: new functional and structural insights. Current Opinion in Chemical Biology, 4, 177–183. doi: 10.1016/S1367-5931(00)00082-X.

Wastney ME, Aamodt RL, Rumble WF, Henkin RI (1986): Kinetic analysis of zinc metabolism and its regulation in normal humans. American Journal of Physiology – Regulatory, Integrative and Comparative Physiology, 251, R398–R408.

Wessells KR, Brown KH (2012): Estimating the global prevalence of zinc deficiency: results based on zinc availability in national food supplies and the prevalence of stunting. PLoS ONE, 7, e50568. doi:10.1371/journal.pone.0050568.

Zhenli LH, Xiaoe EY, Peter JS (2005): Trace elements in agroecosystems and impacts on the environment. Journal of Trace Elements in Medicine and Biology, 19, 125–140. doi: 10.1016/j.jtemb.2005.02.010.

Corresponding Author:

prof. Ing. Ivana J a n k o v s k á, Ph.D.,Czech University of Life Sciences Prague, Faculty of Agrobiology, Food and Natural Resources, Department of Zoology and Fisheries,165 00 Prague-Suchdol, Czech Republic, phone: +420 775 986 602,
e-mail: jankovska@af.czu.cz